DIABETIC RETINOPATHY *
A NEW APPROACH

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THAT the subject of this first lecture dedicated to Dr. Walter Wright may be proportionate to the significance of the occasion and appropriate to the medical fame of Toronto, I have chosen the important problem of diabetic retinopathy, which has assumed, during the hundred years since its recognition, an ever-increasing incidence among the complications of diabetes. Being a condition which tragically and remorselessly affects the eyes of the young subject as well as the old, the careful patient as well as the neglectful, and one which we can neither prevent nor remedy, it is surely one of the more pressing challenges to medical research today. Indeed, it has long excited the interest of workers in many different fields, and various causative hypotheses revolving around a limited number of themes have been emerging in recent years; but it is becoming increasingly clear that none is in harmony with all the known facts, none can be confirmed by animal experimentation, and none has provided a useful line of therapy. I thought it might now be of value to re-examine our knowledge of diabetic retinopathy in an attempt to appreciate which are the important points requiring explanation, and then to consider in what way our present approaches to the problem may be misleading. Finally, I should like to present a concept of the pathogenesis of diabetic retinopathy which has never previously been entertained and which emphasises some of the important possibilities we have so far ignored.

It is known that diabetic retinopathy is usually bilateral, although its severity may differ between the two eyes, and the first abnormality to be noted is the appearance of minute microaneurysms in the posterior polar region of the fundus. Thus they may exist in an otherwise normal retina, but are frequently accompanied and may even be preceded by venous engorgement (Ballantyne 1946, Scott 1951). Œdema is notably absent, but exudates containing abundant lipid gradually appear posteriorly and are particularly related to the microaneurysms, but occur also in regions where they are absent.

New vessel formation may develop at any stage and is of two types: a delicate intravitreal growth where the underlying retinal circulation is inadequate (réte mirabile) (fig. 1), and a coarser growth into organising vitreal hæmorrhages (retinitis proliferans).

As the retinopathy progresses the emphasis of the disease process moves to the arterial side with narrowing of the precapillary arterioles and gradual occlusion of their lumina, resulting in atrophy of the arterial side of the capillary bed and the formation of new channels consisting of dilated irregular vessels on the venous side of the capillary network (Ashton 1953). Fatty degeneration occurs in the anoxic tissue. Complete obliteration of the arterioles eventually results in disappearance of the entire capillary bed.

Cytoid bodies, seen clinically as cotton-wool exudates, may now appear, presumably as a result of the arteriolar changes. It should be stressed, however, that this severe and widespread arteriolar occlusion is not found in hypertension alone and should not be regarded as a superadded complication but as a characteristic late development of the diabetic process. The end stages of the disease, such as retinal detachment and secondary glaucoma, are completely non-specific and do not concern us here.

In summary, then, the following sequence of events requires explanation—venous engorgement, microaneurysms, hæmorrhages, exudates, obliteration of precapillary arterioles and later of capillaries, and lastly new vessel formation. Of these features the appearance of microaneurysms in an otherwise normal fundus is most characteristic of the diabetic state, and it follows that knowledge of their pathogenesis may provide the key to the whole problem of this particular retinopathy, and I therefore propose to discuss them at some length.

Retinal Microaneurysms

Microscopically, microaneurysms are seen to consist of minute spherical or ovoid distensions ranging from 20 to 100 μ in size and are situated mainly on the venous side of the capillary network in the inner nuclear layer of the retina on the course of the capillaries which link the deep and superficial capillary plexuses. It should be noted, however, that the process of aneurysm formation is not peculiar to the venous circulation, for aneurysms may later appear on the arterial side.

Some years ago I drew attention to the remarkable localisation of aneurysms on one side of the capillary only, whereas the opposing wall, apart from showing an indentation, appeared normal (Ashton 1951). By injection and cast techniques it was possible to show that this is due to the fact that the majority of aneurysms arise in small capillary kinks or loops, which either were previously

Fig. 1—Injected diabetic retina showing an intravitreal growth of vessels deflected to expose an underlying zone of capillary obliteration (×9).

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varicose or subsequently became varicose. Exudate containing mucopolysaccharide then oozes through the walls and the two limbs of the loop become adherent and fuse. Thus is produced the typical saccular dilatation which, although appearing to arise from one side of the capillary, in reality derives from degenerative changes involving the entire vessel wall in a sharply demarcated portion.

RELATION TO NEW VESSEL FORMATION

This type of lesion may occasionally be found in other situations, as in the conjunctival vessels or in the growing loops of vascular sprouts in neovascularisation, such as may be seen in the cornea or vitreous. In fact the resemblance is so close that at one time I wondered whether retinal aneurysms might represent arrested new-vessel formations (Ashton 1951). This possibility has recently been fully and carefully explored by Wise (1957) who has firmly concluded that they do indeed indicate an abortive type of neovascularisation and may consequently be found in all situations where retinal anoxia leads to the production of a vasoformative factor.

This may be true; but perhaps the biggest difficulty in accepting this thesis is that, while we have no evidence for assuming that the endothelium of retinal capillaries differs from that elsewhere in the body, microaneurysm formation of the kind seen in the retina is a rarity in other locations, and is not I believe a feature of new vessel formation in anoxic areas in other tissues. Nor have we produced microaneurysms by inducing retinal vaso-proliferation in some hundreds of animal experiments. Moreover, retinal microaneurysms may often exist without an associated neovascularisation, and the converse is also true—which would be surprising if they shared a common origin.

RELATION TO EXTRACELLULAR MICROANEURYSMS

In unravelling the mystery of the retinal micro-aneurysm its uniqueness appears to me to be a clue of great importance. Such microaneurysms do not occur in other organs in diabetes with the possible exception of the kidney: even within the eye they are not found in the iris, ciliary body, or choroid, nor as a rule upon the capillaries growing into the vitreous, even when the retina contains hundreds of aneurysms, and yet these intravitreal vessels are presumably subjected to exactly similar noxious influences as those in the retina. These statements need some modification, for there are two important exceptions.

First, in the conjunctiva, capillary aneurysms have been described by numerous workers (Bajardi 1901, Streiff 1914, Keller 1920, Zeller 1921, Lohlein 1928, Koby 1930) and even thought to be of significance in diabetes (McCulloch and Pashby 1950, Weinstein and Forgacs 1951), but more recent work has shown that they bear no significant relation to the diabetic process itself (Cook 1954).

Secondly, in the renal glomerulus, aneurysmal dilatations have been noted in a variety of diseases both in animals and man and have been demonstrated in diabetic glomerulosclerosis; in fact a common histogenesis between the retinal and renal aneurysms in diabetes has been suspected (Friedenwald 1948, Ashton 1949), and this view has been widely accepted.

RELATION TO DIABETIC GLOMERULOSCLEROSIS

Further investigation of this latter possibility, however, is tending to show that comparison between the retinal and renal lesions is not entirely convincing, there being several points which are difficult to explain on such a basis (Volk 1956, Ashton 1958). For instance, were they both attributable to the same or to a closely related cause, it might be expected that their incidence and degrees of severity would more closely correspond, whereas it is known that retinopathy may exist for many years without the renal complication and its incidence is considerably higher than that of glomerulosclerosis. Nor, when the two lesions coexist, is there any correlation in their degrees of severity (Ashton 1949). Furthermore, retinal micro-aneurysms predominantly affect the venous side of the capillary network and are not confined to diabetes; whereas the renal nodules, being in the glomerular tuft, are arterial lesions and occur only in diabetes. Certainly all experimenters have so far failed to produce retinal and renal lesions together; in fact no-one has succeeded in producing in animals retinopathy which can be accepted as exactly analogous to that seen in human diabetes, whereas several types of lesions resembling glomerulo-sclerosis have been produced by a variety of methods (Ashton 1957).

RELATION TO EXTRAOCULAR VASCULAR DISEASE

The exact relationship between retinopathy and glomerulosclerosis therefore remains an open question, but as more and more data on the retinal microaneurysm accumulate the more strikingly it emerges as a peculiar characteristic lesion of the retina, and less and less ground remains for regarding it as a manifestation of the general vascular disease in diabetes. Identical aneurysms may develop in the retina in the complete absence of extra-ocular vascular disease—e.g., in Eales' disease—and, conversely, generalised arteriosclerotic disease in the non-diabetic subject is not associated with retinal aneurysms. For many years it has been known that microaneurysms are not specific for diabetes, but occur also in a number of unrelated conditions—for example, in central venous occlusion, Eales' disease, Coats' disease, malignant hypertension, and sickle-cell disease—and it is legitimate to seek some common mechanism for their formation, although it must be continually borne in mind that there may be a separate pathogenesis in every case.

These observations may be summarised as follows:

1. Microaneurysms are the earliest and most fundamental lesions of diabetic retinopathy. Elucidation of their pathogenesis may, therefore, provide the answer to the whole problem.
2. With few exceptions, the diabetic type of retinal micro-aneurysm occurs only within the retinal tissue.
3. Retinal microaneurysms although characteristic of diabetes are by no means confined to this disease.
4. They are not necessarily part of a generalised vascular disease.
5. Their development from loop-formations and their location in the posterior fundus mainly in the deep capillary plexus are points of possible importance in pathogenesis.

With this background of information I should like now to consider the present approaches to the problem of pathogenesis of diabetic retinopathy, which may be reviewed under two main headings: (1) intravascular factors, (2) intramural factors.

Intravascular Factors

MICROTHROMBI

Numerous intravascular causes for microaneurysm formation have been recently suggested, but perhaps the clearest example is seen in sickle-cell hæmoglobin-C disease where their appearance is apparently due to anoxia combined with vascular stasis and obstruction from

viscous conglomerates or microthrombi of sickled cells. Why these aneurysms should be confined to the retina is unknown, but its vulnerability has been attributed to the high metabolic rate of the retina which more readily leads to the oxygen depletion favouring sickling (Goodman et al. 1957). The aneurysms seen in retinal venous occlusion, which have also been produced experimentally (Becker and Post 1951), are fundamentally comparable. For this reason intravascular obstructions have been sought in diabetic retinopathy, but none has been found, so the relationship of the above lesions with those in diabetes is still obscure.

LIPIDS AND LIPOPROTEINS

The association between diabetes and a disturbance of fat metabolism has long been recognised and the lipid nature of diabetic vascular changes has been repeatedly emphasised, particularly with regard to retinal and renal lesions. This aspect has recently been studied from two chief points of view—the significance of fat emboli and of lipoproteinæmia.

As regards fat emboli it is interesting that the traumatic variety may produce a fundus picture not unlike that seen in diabetes (Urbanek 1933, Morgan 1949), that fat emboli in choline-deficient rats can give rise to glomerular lesions resembling diabetic glomerulosclerosis (Hartroft 1955), and that fat emboli may be found postmortem more frequently in lungs of diabetics than in those of non-diabetics (Kent 1955). Cook (1956), however, has recently investigated this possibility experimentally, but succeeded in producing lesions which only superficially resembled microaneurysms, and he concluded that fat emboli could not alone be responsible for diabetic retinopathy.

As regards raised levels of lipoprotein in the blood it has been thought that this might be responsible not only for local depositions of fat in the vessel walls but also might give rise to an increased blood viscosity resulting in anoxia from stagnation in the smaller vessels. Important recent work on this aspect of the problem has been carried out by Gofman and his associates (1950a and b) who have studied lipoprotein complexes rather than individual lipids and have separated them by ultracentrifugal methods (Pederson 1945, Lindgren et al. 1950, 1951), and categorised them into ten groups arranged numerically according to their flotation-rates as expressed in Svedberg units (Sf).

In a series of 76 diabetics investigated by Gofman et al. (1950a) the presence of lipoprotein molecules of the Sf 10–20 class showed an increased frequency in diabetic patients and especially in those with vascular complications. Furthermore, it has since been shown that this class of lipoprotein is distinctly related both to diabetic retinopathy (Keiding et al. 1952) and to diabetic glomerulosclerosis (Engelberg et al. 1952) and a causal relationship is thus suggested.

However the amount of lipoproteins of this group is also increased in cases of atheroma in the absence of renal and retinal complications, and also in cases of nephrosis and myxœdema (Gofman et al. 1951), and in malignant hypertensives treated with pyrogens (Lewis and Page 1953) wherein the retina and kidney never present the characteristic pathology of diabetes.

MUCOPOLYSACCHARIDES

Histochemical studies of the retinal and renal lesions of diabetes have led a number of workers to suggest that a disordered metabolism of mucopolysaccharide might be of pathogenic importance (Friedenwald 1948, McManus 1949, Ashton 1949, Warren and Le Compte 1952). As suggested by Gersh and Catchpole (1949) glycoprotein polymers of the ground substance are probably depolymerised by unknown enzymes to form soluble derivatives which diffuse into the blood and so provide the normal serum-mucoprotein.

It would seem possible that an exaggeration of this fundamental process, leading to an abnormal elevation of protein-bound mucopolysaccharide, may underlie the heterogenous manifestations in the diabetic of hyaline deposits in the pancreatic islets, renal glomeruli, and vessel walls, and that involvement of the related carbohydrates in the capillary basement membrane may be responsible for the increased capillary fragility and the formation of microaneurysms.

In fact some workers have found a higher value for protein-bound carbohydrate in the sera of diabetics compared with non-diabetics (Törnblom 1954, Keiding and Tuller 1955) which may show a progressive rise with the onset of retinal, renal, and vascular complications (Berkman et al. 1953, Nielsen and Poulsen 1953, Gilliland et al. 1954, Gilliland and Stanton 1954).

As in the case of lipoproteins, therefore, mucopolysaccharides would appear to be of importance. On the other hand similar blood changes have been reported in the sera of non-diabetics with a large variety of diseases in which retinopathy does not occur, and one is forced to the conclusion that elevation of protein-bound carbohydrate in the blood could not be the only factor in the genesis of this complication. Furthermore, in considering such circulatory factors as raised lipoproteins and mucopolysaccharides, we constantly meet the difficulty of explaining why microaneurysms should be confined to the retina when the whole capillary bed throughout the body must be subjected to very similar influences. Of course, as in the case of sickling, it remains possible that the peculiar metabolic environment of the retina may play a determining role in precipitating substances from the circulation, but we have no evidence that this is so.

Intramural Factors

Factors affecting the vessel walls refer particularly to pathological variations in the calibre of the retinal vessels, whether these changes be functional or structural, and although many theories have been advanced I should select the recent extensive studies of Ditzel and his colleagues as of particular interest (Ditzel 1954a and b, Ditzel and Sagild 1954, Ditzel et al. 1954, Ditzel and Rooth 1955). These workers claim to have found that the conjunctival vessels in the diabetic patient present a characteristic, although not a specific, pattern, consisting of arteriolar constrictions, distortion and irregularity of capillaries, distension and elongation of venules, with œdema and hyaline infiltration of the extravascular tissues. There were also intravascular changes consisting of clumping of red cells with the formation of pseudothromboses or " blood sludging " (Knisely et al. 1947).

They have suggested that these changes might be due to pituitary dysfunction or to variations in oxygen and carbon-dioxide tensions, and, since the pathological pattern was observed in cases of " prediabetes " and even in children of diabetics, there is the important implication that microangiopathy in diabetes may be part of the disease itself rather than a late complication. This concept is attractive in seeking an explanation for anoxia and stasis in the diabetic retina, especially as no structural impedi-

ment to retinal venous outflow has yet been demonstrated; indeed, arguments have been advanced in favour of a functional arteriolar constriction as a precursor of the venous and capillary dilatations (Ashton 1953). Moreover, vasomotor dysfunction of the smaller vessels in diabetes has been previously noted in the retina (Cholst et al. 1952a, b, and c, Sieker et al. 1955) and in the arterioles and capillaries of the extremities (Megibow et al. 1949, Handelsman et al. 1952).

However, if these vascular changes are thought to be responsible for retinopathy it is necessary to explain why no microaneurysms are to be found in the conjunctiva of the diabetic, and, conversely, why no retinopathy is to be found in the small proportion of non-diabetic patients showing this " typical " vascular pattern. Cook (1956), in a preliminary study at the Institute of Ophthalmology, London, has so far failed to confirm the conclusions of Ditzel and his coworkers, but this investigation is not yet comparable in scope with that of Ditzel.

Nevertheless, this brief review of current ideas on the pathogenesis of diabetic retinopathy shows that none quite fits all the facts that need to be explained, and leaves the uneasy feeling that something of vital importance is being overlooked. I should like, therefore, to direct your attention to the possible role of extravascular factors.

Extravascular Factors

Although a certain amount of thought has been given to the possibility that changes in the immediate environment of the retinal vessels might be of importance in the genesis of diabetic retinopathy, such as abnormal fluctuation in intraocular pressure (Poos 1930, Ortiz 1947, 1948, Weinstein 1951), no consideration has been given, as far as I know, to the possible role of the surrounding retinal tissue itself. One would imagine that increases in the volume of cells in densely populated tissues might well have some influence upon the calibre of the capillaries ramifying between them, provided of course that the swelling pressure could rise above that within the vessels, as may be developed osmotically, and provided the pressure could be contained within the tissue, as in organs where there is a fairly rigid capsule or framework. And yet this possibility does not appear to have been explored to any great extent in general pathology although it was clearly advanced by Cannon (1901) in his studies on cerebral contusion. It is only recently that its importance in the retina has been suggested (Ashton, Graymore, and Pedler 1957).

VASO-OBLITERATION DUE TO SWELLING IN THE IMMATURE RETINA

Some years ago when investigating the problem of retrolental fibroplasia, my colleagues and I discovered (Ashton, Ward, and Serpell 1953) that oxygen in high concentrations was able to obliterate vessels within the immature retina of the kitten but not in the mature retina of the cat. We were greatly excited by this finding, for it uncovered a phenomenon the existence of which had not been previously suspected.

The full effect of this peculiar reaction in the retina takes some eight hours to develop, and the main features are as follows. It commences as a pronounced constriction of the arteries and arterioles; the arterioles and the arterial side of the circulation are the first vessels to be obliterated, and this is followed by a gradual disappearance of the whole capillary bed; then the main arteries and finally the main veins close, leaving an apparently avascular retina. It is most important to remember that this reaction is confined to the growing retinal vessels, occurring neither in the other vessels of the eye (even the hyaloid artery when present is totally unaffected) nor in growing vessels as observed in the rabbit cornea, in the rabbit ear chamber, in chick embryos, and cat or rat embryos. Nor indeed—and this perhaps is the most significant fact of all—does it occur in the retinal vessels themselves if the retina should become detached in the course of the experiment. It is also pertinent at this point to recall that transfer of the animal from oxygen to air results in a profuse intraretinal and intravitreal vasoproliferation into those areas where the obliterated retinal vessels were unable to reopen.

Extensive experimental studies we have since carried out have shown that obliteration of the retinal vessels by oxygen is almost certainly not due to a constrictive reaction of the vessels themselves, nor to the removal of a vasodilator substance inherent in the vasoformative process; and these negative conclusions led us to consider the possibility that the vessels may be obliterated by compression through swelling of the surrounding retina.

As a working proposition we postulated that the intracellular fluid content of the retina—let us not at the moment attempt to specify its exact location—might depend upon a dynamic process involving a continuous supply of energy, which in this tissue would presumably derive largely from the breakdown of glucose. We thought, therefore, that interruption of glycolysis might lead to imbibition of fluid into the retina with a consequent rise in intraretinal pressure followed by compression and obliteration of the vessels. The action of well-established glycolytic inhibitors such as sodium fluoride and sodium iodoacetate was therefore investigated.

It was found that both these substances, when injected into the vitreous of the living kitten, gave rise to total obliteration of the retinal vessels in a manner closely resembling that induced by exposure to oxygen; the full effect being achieved by fluoride in about twenty minutes and by iodoacetate in about two minutes. We are now confident that this closure is so intimately related to the retinal swelling that it is almost certainly caused by it, and that oxygen probably achieves its effect in a very similar way. The main supporting facts are as follows:

(1) Vessel closure is accompanied by a milky-white opacification of the retina, and vessels previously near the surface appear to lie in valleys. At the same time a " wire-netting " pattern develops on the retinal surface owing to swelling between the glial network. The order of vessel closure in the fluoride and oxygen effects is identical.

(2) Both the oxygen and fluoride effects are confined to the immature retina, and the sensitive age-groups are similar (Pedler 1959).

(3) Both effects are prevented by retinal detachment, which can most effectively be explained by release or prevention of intraretinal tension.

(4) Both effects may be reversed by the introduction of hypertonic, but not of isotonic, solutions into the vitreous.

(5) Measurement of the retina in histological sections has shown that swelling of the inner layers of the immature but not of the mature retina occurs after the intravitreal injection of sodium fluoride (Pedler 1959).

(6) It has been shown in in-vitro experiments on the kitten and rat retina that when glucose is employed as a substrate, sodium-fluoride inhibition promotes the passage of water into the retina (Graymore 1958, 1959).

It is puzzling that we have as yet found no enzyme poison—or indeed any experimental method—by which

Fig. 2—Injected retina from a case of malignant hypertension showing a "cotton-wool exudate" near the disc. Note that the area of "exudation" is avascular (×25).

vaso-obliteration can be induced in the cat retina, and there are undoubtedly other factors to be discovered before this remarkable difference between the mature and immature retina can be explained. Is there, however, any evidence that vaso-obliteration from retinal swelling might be of importance in the adult retina in disease?

RETINAL SWELLING DUE TO ANOXIA

Consider for a moment the changes observed in the retina in ischæmia. It is well known that after obstruction of the central retinal artery there quite suddenly develops a milky-white opacity of the retina most notable in the posterior pole. This is generally believed to be due to imbibition of fluid into the retina from the osmotic attraction of catalytic products (Duke-Elder 1940)—a belief which largely derives from the work of Loeb (1898), who noted an uptake of water by frog's muscles after ligaturing their blood-supply. Whether this explanation is true or not, here is an example of retinal swelling occurring as a direct result of a deranged metabolism from infarction, which, if the circulation is restored in time, is reversible.

VASO-OBLITERATION DUE TO SWELLING IN THE MATURE RETINA

An exactly analogous process occurs, though on a smaller scale, in so-called "cotton-wool" exudates, as seen, for instance, in malignant hypertension. In sections and flat preparations of the retina it can be readily demonstrated that these lesions are sharply localised areas of retinal swelling in which the nerve-fibre layer is particularly involved. The fibres are thickened and varicose, and show terminal nodal swellings on broken fibres still connected with the ganglion cells; these are thought to form the so-called cytoid bodies characteristic of the cotton-wool lesion.

If one injects with indian-ink the vessels of a retina containing these superficial exudates a surprising picture will be found. They are entirely avascular, as are old anæmic infarcts in the kidney, but the pattern of avascularity within the lesion bears no relation to the field supplied by any retinal vessel. Indeed, it is usually a square or oblong area (fig. 2).

I interpret this picture as meaning that whatever the original cause of the infarction the resulting fluid imbibition and swelling has obliterated the capillaries. Here then in the adult human retina is a miniature replica of the biochemical lesion we can produce with oxygen or fluoride. Moreover, we know that it is due to swelling in the inner retinal layers and that it may be reversible.

RETINAL SWELLING AND MICROANEURYSMS

The next finding of significance in the argument I am developing is the association of microaneurysms with

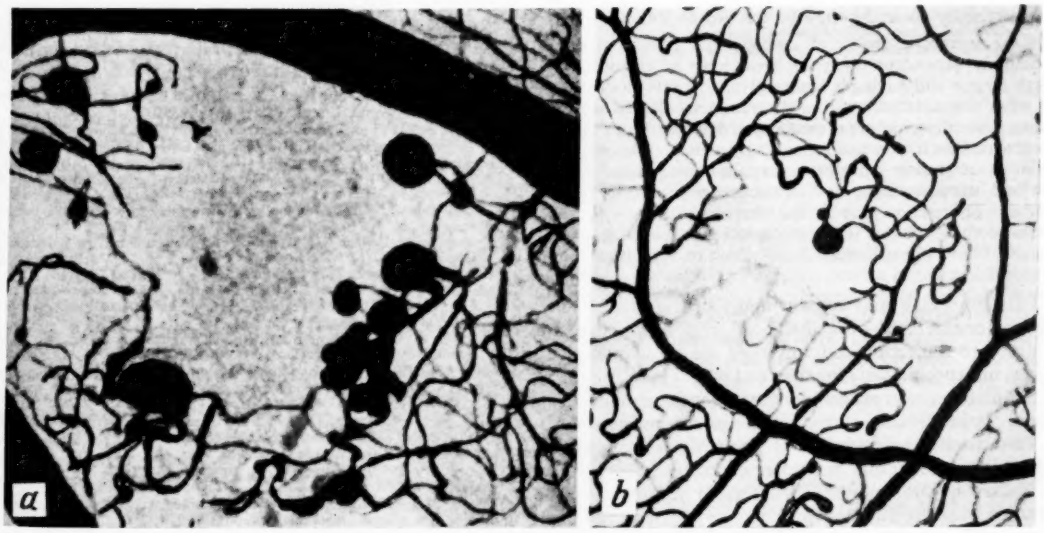

Fig. 3—Injected retina from a case of malignant hypertension showing "cotton-wool exudates" with obliteration of the capillary circulation. Note aneurysm formation at the junction of the normal and avascular tissue. (Fig. 3a ×80; fig. 3b ×55.)

these swollen avascular zones. I have injected retinæ from several cases of malignant hypertension and have frequently found microaneurysms; it is interesting that they were almost always related to cotton-wool exudates and situated at the junction of normal and avascular tissue (fig.3). This picture could, of course, be interpreted in a variety of ways, but it clearly could mean that at the site of aneurysm formation the external pressure in the swollen tissue is insufficient to obliterate the capillary but enough to cause distortion and compression of the vessel and enough to embarrass the circulation to the point of stagnation. Thus, within these small areas in the stratum opticum lies an explanation for loop formation, local blood stagnation, and anoxia, with their sequelæ of capillary dilatation, of microaneurysms, and later of new vessel formation. Hence all these changes, although originated by infarction, could derive solely from external pressure in the swollen retinal tissue. To avoid confusion, I would stress that I am not referring here to passive transudations into the retina, which clearly could not produce pressures greater than those within the vessels from which they arose, but to the active transport of water into the tissues through osmotic pressure which could provide a force amply sufficient to overcome the blood-pressure.

PATHOGENESIS OF DIABETIC RETINOPATHY

Returning now to the problem of diabetic retinopathy it will be seen that the developing sequence of venous engorgement, aneurysm formation, arteriolar constriction, capillary obliteration, and new vessel formation present a chain of events closely, though not perfectly, paralleled by that in the oxygen and fluoride reactions and to some extent in the " cotton-wool " lesion. Is it possible that the diabetic retinal picture which gradually unfolds after many years is essentially of the same nature as that produced experimentally in a matter of minutes or hours in an immature retina by glycolytic inhibitors? I think it is—and this is certainly sufficiently probable to be borne in mind in considering the pathogenesis of diabetic retinopathy.

I therefore suggest that, in future research on this problem, consideration might be given to this concept which broadly speaking may be framed as follows:

In the metabolic defect of diabetes the retina, being so particularly dependent upon the breakdown of glucose as an energy source and having a higher glycolytic rate than almost any other tissue, is subject to a chronic metabolic disturbance leading gradually to failure of osmoregulation with the imbibition of water and an increase in retinal turgescence. The resulting rise in tissue tension impedes the capillary circulation, stagnation and anoxia result, and microaneurysms form. The arteriolar obliteration may be the late results of this process, but here the problem is more complicated since arteriolosclerosis and hypertension have also to be taken into consideration.

This concept would explain many of the facts I have already enumerated—for instance, why aneurysms are confined to the retina and why they are so characteristic of, yet not specific for, diabetes, and why " good " control of the diabetes over many years may have some beneficial effect. It implies, of course, that diabetic retinopathy—at least in its early stages—is primarily a neurological disease, the manifest vascular changes being purely secondary developments. Considerable argument can be advanced against the concept, however; perhaps the most pertinent is our failure to produce retinal swelling in the adult animal, but experimental work on this aspect is still in its very early stages. Nor can any increase in fluid be detected ophthalmoscopically in the retina in diabetic retinopathy, but this may possibly be explained by the chronicity and mildness of the process.

I make no attempt to minimise these difficulties, for this concept is no pretence at a final solution, but is intended merely to attract attention to some new factors of possible importance, for I believe that somewhere within its framework may lie the answer not only to the problem of diabetic retinopathy, but also to the wider question of the interrelationships in pathogenesis between the vascular retinopathies.

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THE SURGICAL RELIEF OF CHRONIC MYOCARDIAL ISCHÆMIA

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DURING the past 30 years various surgical measures have been elaborated from animal experiments in an attempt to increase the blood-supply to the ischæmic myocardium, by the development of a collateral circulation, and thereby to counteract the effects of coronary atherosclerosis. Chemical irritants have been introduced into the pericardial sac (Beck 1929), or mechanical abrasion and the insufflation of bone dust (King 1941) have been used to excite an inflammatory response and produce vascular adhesions. Cardio-omentopexy (Beck and Tichy 1935, Beck et al. 1935, O'Shaughnessy 1936, 1937, Feil and Beck 1937, Mason 1937), or grafts of pectoral muscle (Beck 1935, 1936a, and b) have sought to bring a fresh blood-supply to the myocardium.

More recently a combination of abrasion of the parietal pericardium and epicardium, the introduction of asbestos dust into the pericardial sac, and the narrowing of the coronary sinus by ligature has yielded satisfactory results (Beck and Brofman 1956, Beck et al. 1958). Blalock (1958) suggests that the results are similar for several different procedures.

There is no satisfactory evidence that any of the many operations used to bring a new blood-supply to the heart by formation of adhesions can be effective. Indeed, any evidence there is points to the contrary. At later operations on the heart, when the pericardium is always obliterated, the numerous adhesions never contain any blood-vessels. We have therefore been unwilling to accept that this type of operation has any rational basis. Recently Beck himself has declared that there is no evidence that it is possible to bring a new blood-supply to the heart from outside. On the other hand he suggests that, as a result of the various irritative processes to which the myocardium is subjected in these procedures, the inter-coronary anastomoses are improved and a more favourable distribution of blood within the myocardium is produced. This concept appeals to us, and we have planned a simple procedure of abrading the parietal and visceral pericardium to try to produce a myocardial reaction sufficiently brisk to improve the inter-coronary anastomoses in this way. We report here the postoperative progress of ten patients with very severe angina pectoris in whom this procedure has been performed.

Methods

Selection of Patients

Our indication for operation was progressive and incapacitating angina; unresponsiveness to medical treatment; no marked cardiac enlargement; and freedom from cardiac failure, severe hypertension, and generalised arterial disease. All patients had been treated with coronary vasodilators and bed rest, some with analgesics such as iproniazid, others with long courses of anticoagulants or hypotensive drugs as well. In each the problem was of overwhelming myocardial ischæmia.

Assessment of Patients

Besides a detailed history and examination, particular attention was paid to the blood-count, erythrocyte sedimentation-rate, serum-cholesterol, blood Wassermann and Kahn reactions, radiography of the chest, and electrocardiography (E.C.G.). All patients were closely observed for 4 weeks or more before operation. The exercise tolerance of each patient was assessed before and after operation from the history and by means of a standard exercise test under stable conditions; a twelve-lead E.C.G. was taken before and after the exercise. Under supervision the patient was encouraged to continue to the production of pain, dyspnœa, or fatigue, and his symptoms were recorded. Such assessment was repeated 2, 4, and 6 months after operation.

The patients were digitalised before operation and throughout the immediate postoperative period.

Case-histories

Case 1.—Mr. A., aged 51. Family story of hypertension. Coronary thrombosis September, 1956, since when progressive angina of effort. Blood-pressure (B.P.) 150/90. Cholesterol 310 mg. per 100 ml. Cardiac/thoracic ratio (C.T.R.) 13/30·5.

E.C.G. showed posterior myocardial infarction with iso-electric ST segments. Exercise E.C.G.: positive after 3 minutes' exertion with marked ST shift over left ventricle (fig. 1).

Operation (July 14, 1958).—Coronary arteries showed greyish sclerosis and felt hard, particularly the descending

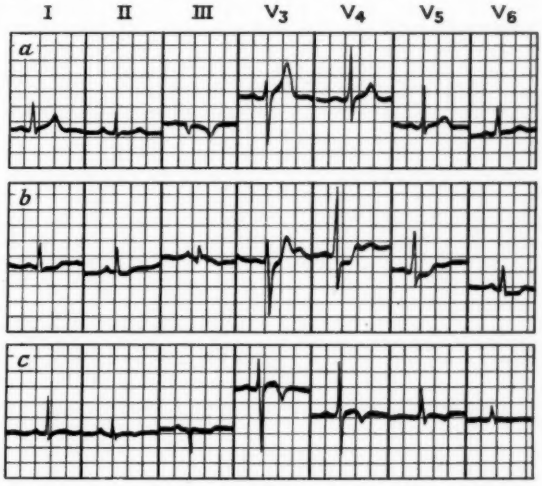

Fig. 1—Case 1. E.C.G. leads I-III and V_{3-6}: *a* before and *b* after exercise showing typical ischæmic ST-segment depression, while *c* shows ST and T changes in the precordial leads 2 months after operation.

branch of the left coronary for 1 cm. near its origin. There were a number of dense white scars on the posterior aspect of the left ventricle. The visceral and parietal pericardium was scraped. Mediastinal fat was sutured in close contact with the heart. The left internal mammary artery was ligated in the 5th space and coagulated in the 2nd space.

E.C.G. (2 months after operation) showed an anterolateral reaction similar to that of infarction (fig. 1). 6 months after operation this anterior-infarction pattern persisted. 5 minutes' exercise at 4 months and 10 minutes' at 6 months did not cause pain and produced only slight ST shift. In May, 1959, he was working whole time as a bank clerk. Occasionally he had minor substernal tightness with considerable exertion.

Case 2.—Mr. B., aged 55. Developed angina of effort in 1954, and in August, 1955, a posterior myocardial infarction with subsequent congestive failure. Unable to work because of increasing angina of effort. B.P. 140/80. Cholesterol 312 mg. per 100 ml. C.T.R. 12·5/27·5.

E.C.G. showed posterior myocardial infarction. Exercise E.C.G.: positive after $1^1/_2$ minutes exertion, ST shift in V_2 and V_3 becoming more marked.

Operation (July 14, 1958).—The coronary vessels were obviously abnormal, thickening with some calcification being

felt in the upper part of the descending branch of the left coronary artery. The posterior aspect of the left ventricle showed many dense white flame-shaped scars. The visceral and parietal pericardium was curetted, and the mediastinal pleura sewn over the unsutured pericardial wound. The left internal mammary was ligated in the 5th interspace and coagulated in the 2nd space.

E.C.G. (2 months after operation) showed T-wave inversion in V_3 and V_4, rather less after exercise. 4 and 5 months after operation he managed 3 and 4 minutes' exercise with slight fatigue and some dyspnœa, but no pain, and the inverted T waves in V_3 and V_4 became upright.

In March, 1959, he was very much better, getting slight angina only with postprandial exertion, although he was not working. At the end of May he was free from pain with normal activity, and there was less cardiographic ischæmia with exertion.

Case 3.—Mr. C., aged 42. Family history of hypertension. Coronary thrombosis March, 1957, since when angina of effort had prevented his working as a bus conductor. The pain was unusual in that it persisted from $^1/_2$ to 1 hour in spite of rest. B.P. 120/90. Cholesterol 295 mg. per 100 ml. C.T.R. 15·5/31.

E.C.G. showed an extensive anterior myocardial infarction. Exercise E.C.G.; no further changes and no pain although considerable fatigue occurred at 3 minutes.

Operation (*Sept. 9, 1958*).—A scar (8 × 6 cm.) occupied the anterior aspect of the heart. Along the left border and at the extreme apex pink muscle could be seen, but the scarred area extended 3 cm. along the left descending branch. This artery was small and solid. Around the edge of the scar there were white and streaky pink areas with some streakiness on the posterior aspect of the heart. None of this area contracted during systole. There were some filamentous adhesions over the two areas, each about 1 sq. cm. which seemed avascular, although a few seconds after cutting a little blood appeared on the cardiac end, showing that they contained tiny vessels. The whole visceral and parietal pericardium was curetted in the usual way and closed by suturing pericardial fat.

E.C.G. (2 months after operation) showed T-wave inversion in V_2, V_3, and V_4 and less ischæmia over the tip of the left ventricle. After 5 minutes' exercise without pain the T-wave inversion had disappeared, although of course the Q waves remained. At 4 and 6 months T-wave inversion was present before and with exercise.

In April, 1959, he was working at home as a clock repairer. He had slight pain in both axillæ when unduly tired, but no pain with walking. In July he was symptom free.

Case 4.—Mr. D., aged 59. Angina of effort began in 1947 while cycling to work, and became progressively worse. In December, 1957, the pain was occurring at rest. B.P. 180/120 (preoperatively the patient was treated with hypotensive drugs). Cholesterol 300 mg. per 100 ml. C.T.R. 13/28·5.

E.C.G. normal. Exercise E.C.G. showed ST-segment shift over the left ventricle in a vertical heart. Pain occurred after 1 minute.

Operation (*Sept. 1, 1958*).—There was one streaky fibrous area high at the back. The descending left coronary artery was obviously atheromatous. At the site of origin of the circumflex artery there was a firm nodule, which might have been an atheromatous plaque or a thrombus. The visceral and parietal pericardium was curetted, and was left open as there was not enough fat to approximate.

E.C.G. 2 months after operation (fig. 2) showed T-wave inversion in V_2, V_3, and V_4. With exercise the T waves in V_2, V_3, and V_4 became upright and there was remarkable elevation of the ST junction in V_2 and V_3—10 mm. in V_3. At 4 months pain occurred after 3 minutes' exercise, and at 6 months there was no symptomatic improvement, although less change in the E.C.G.; there were, however, many ventricular premature beats after exercise.

In March he was given digoxin apparently with symptomatic improvement; but improvement is slight and represented by a daily intake of 3–4 nitroglycerine tablets compared with 15 before operation.

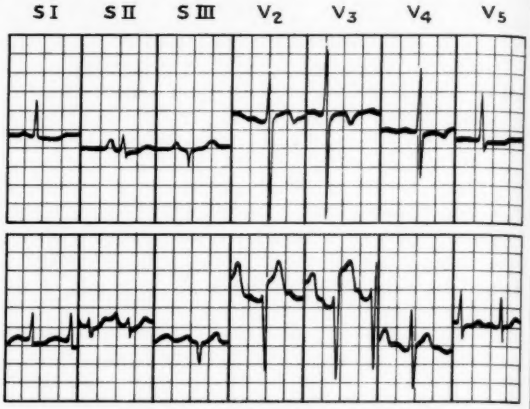

Fig. 2—Case 4. E.C.G. showing the myocardial reaction in V_2-V_5 2 months after operation; note the upright T and marked ST elevation in these leads following exercise.

In May he was able to walk 500 yards without pain and was rather better.

Case 5.—Mr. E., aged 47.—Had angina of effort since June, 1956. In January, 1958, the E.C.G. suggested a small posterior myocardial infarction. The angina became progressively more severe and finally recurred at rest. B.P. 140/85. Cholesterol 325 mg. per 100 ml. C.T.R. 14/32.

E.C.G. showed very minor ischæmic changes over the left ventricle. Exercise E.C.G. revealed marked ST-segment depression over the left ventricle (4 mm. in V_4–V_5) with typical pain in 3 minutes.

Operation (*Oct. 27, 1958*).—The anterior aspect of the heart and region of the apex showed less contraction than adjacent muscle. The descending left coronary artery was a thin opaque thread, but no block was felt. The myocardium looked reasonably healthy. The epicardium and serous pericardium were abraded. Fat removed from around descending left coronary artery. Left internal mammary artery coagulated in 4th space.

No E.C.G. was performed 2 months after operation on account of osteomyelitis of a rib. At 4 months T waves were of small potential in the standard leads, and there was T inversion at rest in V_3 and V_4; 5 minutes' exercise produced slight soreness in the throat and moderate dyspnœa; ST-segment shift over the left ventricle was marked, concurrently the T waves in V_3 and V_4 became upright.

In April he reported himself as very well. After two flights of stairs he developed pain. There had been apparent help from digoxin. In June he was working as a telephonist and was able to walk four miles without pain.

Case 6.—Mr. F., aged 62.—In 1948 the blood-pressure was 270/120 in association with unilateral chronic pyelonephritis and renal lithiasis. Following nephrectomy the blood-pressure remained at 180/110. In 1955 angina of effort appeared and became so severe that in April, 1958, he was admitted to hospital, where he developed pulmonary infarction following a deep crural vein thrombosis. The hypertension was controlled by reserpine and mecamylamine, but the angina remained most severe. Cholesterol 340 mg. per 100 ml. C.T.R. 13·5/30.

E.C.G. showed left bundle-branch block. Exercise E.C.G. showed no change. Pain occurred within 3 minutes.

Operation (*Oct. 28, 1958*).—The pericardium was tense. The myocardium looked normal. The descending branch of the left coronary artery was grossly abnormal owing to calcification; it felt rigid and possibly solid for about four cm., although the distal part was still shortening with the heart beat. Formal curettage of the epicardium and pericardium was performed and the pericardial incision covered with fat.

There was congestive failure for a few days in early convalescence.

E.C.G. 2 and 4 months after operation did not show any material change other than some deformity of the ST segment

in V_3 at rest. At 2 months there was slight precordial pain after 3 minutes' exercise and a little less at 4 months. In April he had no pain with walking and was actively employed as a commissionaire. At the end of May he had no pain whatsoever and no undue dyspnœa. He walks with a military step, gardens, and covers four miles without pain.

Case 7.—Mr. G., aged 57. Angina of effort began in early 1957. In August, 1957, the condition was worse, and during 1958 he became restricted to 20 yards' brisk walking, and was markedly depressed. B.P. 150/90. Cholesterol 460 mg. per 100 ml. C.T.R. 13/28.

E.C.G. showed ST-segment depression over the left ventricle. Exercise E.C.G. showed rather more ST shift. Pain was brought on in $1^1/_2$ minutes.

Operation (*Dec. 22, 1958*).—The heart muscle appeared normal except for one peculiar area 1 cm. in diameter on the anterior apical aspect, which looked bruised; its dark red colour was either from extravasated blood or a collection of small vessels. The left coronary artery was rigid almost to the apex. The epicardium and parietal pericardium were abraded.

E.C.G. at 2 months after operation showed rather more ischæmic change, in turn more with exercise. Breathlessness limited the test to $2^1/_2$ minutes. At 4 months the ischæmia on effort was less and dyspnœa was less readily produced.

In April he reported himself as very well and free from pain, despite quite considerable exertion; concurrently the change in his personality has happily been most marked and equally for the better. In June he was working as a lavatory attendant. He exercised for 5 minutes with only slight substernal soreness.

Case 8.—Mr. H., aged 53. Family history of coronary-artery disease. Sudden onset of angina of effort in September, 1957, which became progressively worse in spite of 3 months' rest and 3 weeks' treatment with anticoagulants. In August, 1958, he could walk a mile, but in December was limited to 30–200 yards on the level. Occasionally pain was occurring at rest without obvious emotion as a precipitant. B.P. 155/95. Cholesterol 235 mg. per 100 ml. C.T.R. 14·5/29·5.

E.C.G. January, 1959; T inversion in lead III and IIIR but upright in avF and avL. Some oblique depression of the ST segments in V_4 and V_5. Exercise E.C.G. showed typical ischæmic changes over the left ventricle. Pain occurred in $1^1/_2$ minutes.

Operation (*Jan. 17, 1959*). The myocardium looked normal, but the left coronary artery was atheromatous; the common stem, the circumflex branch, and the proximal descending branch were all unduly firm and easily felt. The visceral and parietal pericardium was abraded; mediastinal fat was sutured over the pericardial defect. The left internal mammary artery was coagulated.

E.C.G. at 2 months after operation showed T inversion in I, avL, and V_3, V_4, and V_5: the ST segments were depressed in V_6 and V_7 with exercise.

At 4 months there was less T inversion in V_3 and V_4 but more ischæmic ST shift over the left ventricle; after $3^1/_2$ minutes' exercise he developed pain with slightly more ST depression.

He was back at office work 2 months after operation, and at 4 months was able to walk $1^1/_2$ miles on the level without pain. He had used two nitroglycerine tablets in the previous 2 months.

Case 9.—Dr. J., aged 61.—Coronary occlusion in February, 1955, since when undue dyspnœa with slight exertion. In November, 1956, he had a further coronary occlusion, followed by increasing angina of effort. In February, 1957, he developed acute left ventricular failure which resolved with treatment, but the angina became more troublesome. He was on continuous anticoagulant therapy from November, 1956. B.P. 140/80. Cholesterol 250 mg. per 100 ml. C.T.R. 16/33.

E.C.G. October, 1958, showed a full thickness anterolateral infarction with isoelectric ST segments.

Operation (*Oct. 6, 1958*).—There was an infarction some 8 cm. in diameter in the anterior apical region. The myocardium was partly opaque and showed numerous new formed small vessels. The rest of the muscle was rather thickened. The anterior descending coronary artery seemed solid for 2–5 cm. below its origin. As much of the ventricular area as possible and the parietal pericardium were roughly curetted.

4 months after the operation there was much improvement, and at 6 months he was practising medicine without restriction of his activities. Angina was present only during rare bouts of rapid palpitation, which were controlled by digitalis.

E.C.G. 6 months postoperatively showed the QS pattern of anterior infarction with elevation of the ST segments: after 5 minutes' exercise, which caused some dyspnœa and slight discomfort in the throat, the T waves became upright over the "infarcted" area.

Case 10.—Mr. K., aged 54.—Family history of coronary-artery disease. Coronary thrombosis in 1954. In November, 1957, he complained of angina of effort which became rapidly and progressively worse, lasting on occasions for 1 hour. Pre-operatively limited to 15 yards on the level. B.P. 125/80. Cholesterol 270 mg. per 100 ml. C.T.R. 14/29·5.

E.C.G. February and March, 1958, minor ST-segment depression in V_5, otherwise normal. March, 1959, rather more ischæmic depression over the left ventricle and small Q in III and avF. Exercise E.C.G. (3 minutes slowly), on March 6, 1959, showed marked ST-segment depression and T-wave changes over the left ventricle which reverted after 10 minutes.

Operation (*March 12, 1959*).—The pericardium was tense and contained a considerable excess of bloodstained fluid, some days old. The left ventricle showed white fibrous areas ($0{\cdot}5 \times 0{\cdot}2$ cm.) on both anterior and posterior surfaces. The main left coronary artery felt solid for 2 cm. from its origin. The whole visceral and parietal pericardium was abraded.

After operation his condition was satisfactory until evening when the blood-pressure suddenly fell to 80 mm. Hg, and he died within the hour. Necropsy showed severe occlusion of coronary arteries by atheroma, but no recent thrombosis. There were multiple small areas of old fibrosis in the left ventricle and two yellowish areas in the upper and lower ventricular septum, which on microscopy showed small areas of recent infarction.

Discussion

The most recent patient is included to emphasise that operation is not without danger, and that myocardial infarction may occur without signs or symptoms differing from those of relative ischæmia of a more temporary nature. This is, however, the only death in the series, which is larger than described, for assessment early is difficult.

In only three patients did angina of effort directly follow a definite myocardial infarction (cases 1, 3, and 9), but in two others infarction followed the angina of effort (cases 2 and 5), and in case 10 infarction antedated the effort angina by 3 years. In all the angina was outstandingly severe, progressive (despite bed rest), and uncontrolled by treatment; in some it was occurring at rest or responding very slowly to rest. Pain was produced by set exercise lasting 1–3 minutes, in all except case 3, in whom pain was only very slowly relieved by rest and in whom considerable effort was thought unsafe. E.C.G.s taken before operation correlated well with the operative findings, except that actual myocardial damage was more extensive than had been thought. No patient had gross cardiac enlargement, cardiac failure, or uncontrollable hypertension before operation. The serum-cholesterol ranged from 235 to 460 mg. per 100 ml. (case 7) but averaged 290.

Of the nine survivors, case 1 is outstanding, working full time and quite free from angina with ordinary activity; 10 minutes' exercise failed to produce pain 6 months after operation. The condition of two other patients has improved strikingly, while the results may be classed as good in a further five cases. In one patient (case 4) improvement is slight or absent.

Whereas ST-segment depression over the left ventricle with exertion is a reliable measure of myocardial ischæmia (fig. 1), serial E.C.G.s in these few patients have been of

interest, but of little value in the assessment of myocardial blood-supply after operation. Abrasion of the epicardium and parietal pericardium produces the appearance of lateral wall infarction in V_3 and V_4 (fig. 2), and pre-operative occlusive episodes and digitalis may further confuse the picture. It is notable that the inverted lateral-wall T wave seen after operation may become positive with exercise, and its ST segment may simultaneously become elevated. Accordingly, the assessment of these patients has been mainly on clinical evidence. The psychological effects of special investigation and operation and follow-up must be considerable, yet improvement in pain and dyspnœa on effort has been most after 4 months, when such effects would be expected to be waning, if not already absent. Fatigue has been a particular complaint in early convalescence, although only one patient (case 6) developed right ventricular failure in the immediate postoperative period. In this instance, however, the failure cleared up within 3 weeks.

Summary

The progress of ten men with intractable angina pectoris treated by abrasion of the epicardium and parietal pericardium has been described. Postoperative assessment has been mainly clinical; the results at 6 months are quite excellent in three patients, good in five, and poor in one. There was one death.

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FOLIC-ACID DEFICIENCY IN PREGNANCY
THE PATHOGENESIS OF MEGALOBLASTIC ANÆMIA OF PREGNANCY

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MEGALOBLASTIC anæmia is commonly associated with pregnancy, and its incidence is not less than 2·8% of all pregnancies (Giles and Shuttleworth 1958). The anæmia responds to folic acid (Moore et al. 1945) and its appearance in pregnancy may be prevented by giving folic-acid supplements (Lowenstein et al. 1955). This suggests that megaloblastic anæmia in pregnancy is due either to deficiency of folic acid or to interference with the utilisation of this vitamin in pregnancy (Badenoch et al. 1955, Girdwood 1956).

In the work reported here we have sought to confirm earlier observations that megaloblastic anæmia of pregnancy is associated with folic-acid deficiency (Chanarin et al. 1958b), to determine whether similar or lesser degrees of folic-acid deficiency appear in the course of normal pregnancy, and, finally, to determine the factors in pregnancy producing folic-acid deficiency.

Methods

Assessment of Folic-acid Deficiency

This was assessed by measuring the rate of clearance from the plasma of injected folic acid (Chanarin et al. 1958c). A dose of 15 μg. of folic acid per kg. of body-weight was given intravenously and the serum-folic-acid concentrations measured 3, 15, and 30 minutes after the injection. In 50 healthy subjects, both male and female, the plasma levels at these times were as follows:

Minutes	*μmg. per ml.*
3	75–186 (mean 127±14)
15	21–80 (mean 40±2)
30	4–49 (mean 20±9)

In the presence of folic-acid deficiency the test dose of folic acid is cleared from the plasma into the tissues more rapidly and the plasma-folic-acid concentration at these times is lower than in the control subjects.

Folic-acid Absorption Test

This was carried out by giving an oral dose of 40 μg. of folic acid per kg. of body-weight and measuring the serum-folic-acid content 1 and 2 hours after the dose (Chanarin et al. 1959). Normal subjects showed a peak serum level of folic acid which was greater than 40 μmg. per ml.

Absorption tests were carried out after the subject had been previously "saturated" by giving 15 mg. of folic acid intramuscularly daily for 4 days. The test was carried out 36 hours later when the injected folic acid had been cleared from the plasma. After "saturation" in this manner normal subjects and patients with megaloblastic anæmia clear folic acid from the plasma more slowly than do subjects not "saturated" in this way (Chanarin et al. 1958c). Absorption tests on patients with megaloblastic anæmia were carried out after the maximum reticulocyte response had occurred.

Measurement of Folic Acid in Serum

The folic-acid content of serum in both the clearance and absorption tests was measured by microbiological assay using *Streptococcus fæcalis* (A.T.C.C. 8043) as the test organism (Toepfer et al. 1951, Chanarin et al. 1958a).

Subjects Studied

Folic-acid-clearance tests were carried out on the following groups:

(1) 30 control subjects, who were healthy women between the ages of 18 and 40.

(2) 250 pregnant women without anæmia. The duration of pregnancy in these women at the time of the test is shown in table I. The majority of these subjects were tested while attending the antenatal clinic; the rest had been admitted for minor degrees of toxæmia, or were awaiting the onset of labour. The duration of pregnancy was calculated from the date of the

TABLE I—DURATION OF PREGNANCY IN 250 PREGNANT WOMEN ON WHOM FOLIC-ACID-CLEARANCE TESTS WERE CARRIED OUT

Duration of pregnancy (weeks)	No. of patients
12	12
13–16	27
17–20	28
21–24	31
25–28	27
29–32	30
33–36	30
37–40	31
Full term	25
43–45	9

last menstrual period, the size of the uterus on bimanual examination at the first attendance, and the height of the fundus on subsequent regular examination at the antenatal clinic.

(3) 11 patients with normal twin pregnancy, 34 to 39 weeks pregnant.

(4) 11 patients with untreated megaloblastic anæmia of pregnancy. The diagnosis of megaloblastic anæmia was made by sternal-marrow aspiration. Further details of these patients are given in table II.

Folic-acid-absorption tests were carried out on the following groups:

(1) 90 healthy subjects of both sexes.

(2) 45 women who were between 20 and 40 weeks pregnant.

(3) 10 women with treated megaloblastic anæmia in pregnancy.

Results

FOLIC-ACID CLEARANCE IN PREGNANCY

The mean and range of the serum-folic-acid concentrations 3, 15, and 30 minutes after the injection of the test dose in normal and pregnant subjects are shown in table III. The serum-folic-acid levels found 15 minutes after the injection in the different groups are compared in fig. 1.

TABLE II—FOLIC-ACID-CLEARANCE TEST IN 11 PATIENTS WITH UNTREATED MEGALOBLASTIC ANÆMIA OF PREGNANCY

Case no.	State of pregnancy (weeks)	Hæmoglobin (g./100 ml.)	Serum-vitamin-B_{12} (μμg./ml.)	Serum-folic-acid (μmg./ml.)		
				3 min.	15 min.	30 min.
1	38	6·3	115	4	0	0
2	28	3·3	200	9	0	0
3	3 after delivery	8·4	110	30	0	0
4	36	7·8	135	41	0	0
5	37	9·1	135	43	0	0
6*	35	4·3	125	43	0	0
7	5 after delivery	4·0	105	52	0	0
8	6 after delivery	9·0	620	58	0	0
9	24	9·6	230	60	9	0
10*	36	8·8	160	62	8	0
11	36	7·6	170	64	0	0

* Twin pregnancy.

Normal Pregnancy

Injected folic acid was cleared more rapidly in pregnancy than in non-pregnant healthy subjects.

Before the 12th week the mean serum-folic-acid levels after the intravenous injection were already significantly lower than in normal controls ($P=0.001$). Thereafter, the rate of clearance of injected folic acid became increasingly more rapid from the 12th to the 36th week. The fall in the mean serum-folic-acid concentration throughout pregnancy was significant ($P=0.01$). The rate of clearance was most rapid between the 37th and 40th weeks.

At full term the rate of clearance of injected folic acid, although still more rapid than in early pregnancy, was significantly slower than in subjects 37–40 weeks pregnant ($P=0.001$). The rate of clearance appeared to be still slower in 9 pregnant women who were tested 3–5 weeks after their expected date of delivery, although the difference between this group and the patients at full term was not statistically significant.

Twin Pregnancy

The clearance of injected folic acid was more rapid in this group than in single pregnancy ($P=0.001$). The mean serum-folic-acid levels 3, 15, and 30 minutes after the intravenous injection in patients with twin pregnancy were 67, 8, and 0 μmg. per ml., compared with 91, 19, and 5 μmg. per ml. in a group of patients with single pregnancy at a corresponding period of gestation.

TABLE III—FOLIC-ACID-CLEARANCE TEST IN PREGNANCY

State of pregnancy (weeks)	Serum-folic-acid (μmg. per ml.)					
	3 minutes		15 minutes		30 minutes	
	Mean ± S.E.	Range	Mean	Range	Mean	Range
Normal subjects:	131 ± 6	80–186	43 ± 3	21–80	21 ± 2	4–44
Pregnant women:						
12	104 ± 8	70–148	28 ± 2	15–40	11 ± 1	6–19
13–16 ..	99 ± 6	45–170	27 ± 2	10–44	11 ± 1	0–26
17–20 ..	94 ± 5	63–170	26 ± 2	12–50	9 ± 1	0–28
21–24 ..	93 ± 3	50–135	25 ± 2	9–48	8 ± 1	0–23
25–28 ..	91 ± 4	53–136	24 ± 2	7–52	8 ± 1	0–22
29–32 ..	95 ± 5	55–162	23 ± 2	6–58	6 ± 0	0–27
33–36 ..	98 ± 5	53–179	22 ± 2	10–36	6 ± 2	0–15
37–40 ..	84 ± 13	51–135	17 ± 1	6–30	4 ± 0	0–12
Full term ..	97 ± 4	44–135	25 ± 2	5–44	17 ± 1	0–21
43–45 ..	104 ± 6	84–136	30 ± 5	16–62	10 ± 2	0–21
Twins ..	67 ± 8	40–110	8 ± 2	0–18	0	0–4
Megaloblastic anæmia of pregnancy ..	42 ± 11	4–64	2 ± 1	0–9	0	..

The clearance in every patient with twin pregnancy was more rapid than normal (fig. 2), and in 3 patients no folic acid remained in the plasma 15 minutes after the injection.

Megaloblastic Anæmia of Pregnancy

The rate of clearance of folic acid was most rapid in this group, and in every patient the rate of clearance of injected folic acid was more rapid than normal (table II and fig. 3). The serum-folic-acid levels 3 minutes after the injection ranged from 4 to 64 μmg. per ml. (mean 42 ± 11 μmg per ml.), and in 9 out of 11 of the patients the folic acid had been completely cleared from the plasma by the time the 15-minute blood sample had been taken.

Although the rate of clearance of folic acid was increased in many women with normal single pregnancy, none of

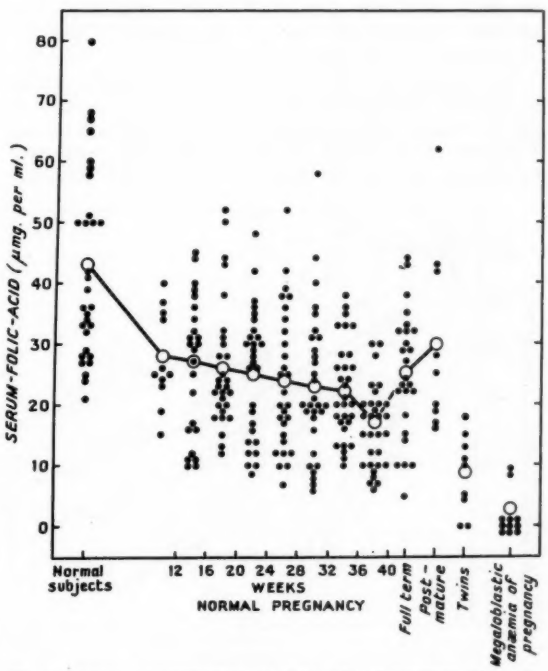

Fig. 1—Serum concentration of folic acid 15 minutes after an intravenous injection of 15 μg. of folic acid per kg. of body-weight in 30 normal subjects, 250 pregnant women, 9 women with twin pregnancy, and 11 patients with untreated megaloblastic anæmia of pregnancy. The open circles indicate the mean serum-folic-acid concentrations in these groups.

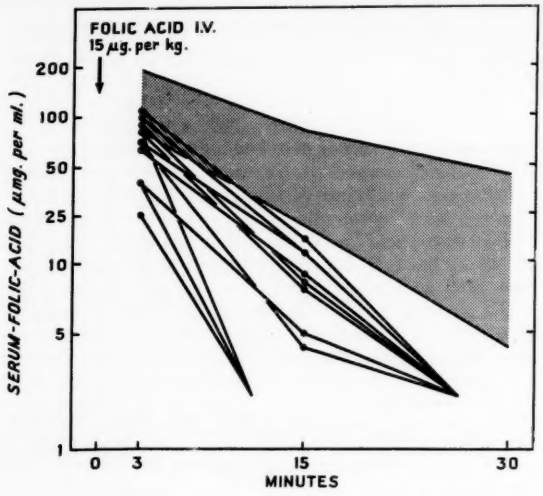

Fig. 2—Serum-folic-acid concentrations, after the intravenous injection of 15 µg per kg., in 11 women with normal twin pregnancy. The stippled area represents the range of clearance in 30 healthy non-pregnant women.

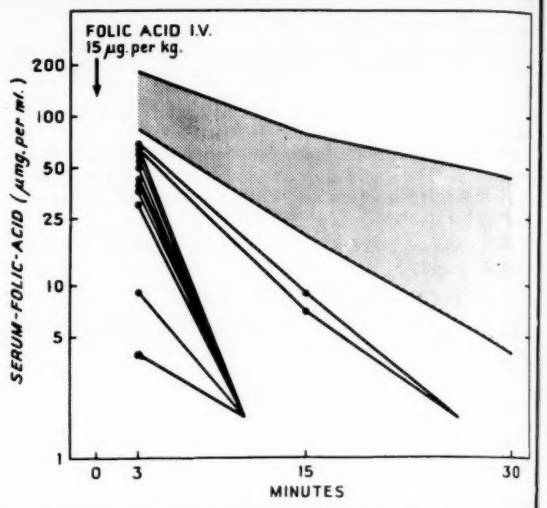

Fig. 3—Serum-folic-acid concentration, after the intravenous injection of 15 µg. per kg., in 11 patients with untreated megaloblastic anæmia of pregnancy. The stippled area represents the range of clearance in 30 healthy non-pregnant women.

these cleared folic acid as rapidly as most patients with megaloblastic anæmia of pregnancy or as some patients with twin pregnancy. Thus folic acid was still present, though in reduced amount, in the 15-minute sample of the patients with uncomplicated pregnancy.

The results of the folic-acid clearance test in pregnancy have been summarised in fig. 4, which compares the mean serum-folic-acid concentration after the injection in mid- and late pregnancy, twin pregnancy, and untreated megaloblastic anæmia of pregnancy with the clearance in normal subjects.

The percentage of abnormal folic-acid-clearance tests at different stages of pregnancy are compared in table IV and fig. 5 with the growth increment of the fœtus (Streeter 1920) and of the uterus (Gillespie 1950). There is a good correlation between the incidence of abnormal clearance tests and the rate of growth of the fœtus and uterus. Before the 12th week only 1 of 12 clearances (8%) was more rapid than normal. Thereafter the percentage of abnormal tests increased from 26 in weeks 13–16 to 68 in weeks 37–40. The very high incidence of abnormal results in the last month (68%) coincides with the most rapid growth of the fœtus, a period during which its weight increased by a third.

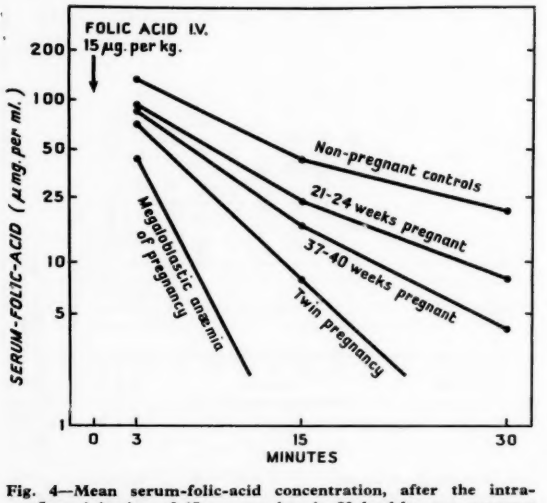

Fig. 4—Mean serum-folic-acid concentration, after the intravenous injection of 15 µg. per kg., in 30 healthy non-pregnant women, 31 women 21–24 weeks pregnant, 31 women 37–40 weeks pregnant, 11 women with twin pregnancy, and 11 patients with megaloblastic anæmia of pregnancy.

ABSORPTION OF FOLIC ACID IN PREGNANCY

The peak serum-folic-acid concentration after an oral dose of folic acid in 90 normal controls ranged from 42 to 186 µmg. per ml. (mean 95±9), and the peak serum concentration in 45 pregnant patients was significantly lower, ranging from 11 to 86 µmg. per ml. with a mean of 48±3 (P=0·001). These results are shown in fig. 6.

TABLE IV—INCIDENCE OF RAPID FOLIC-ACID-CLEARANCE TESTS IN PREGNANCY

State of pregnancy (weeks)	Rapid folic-acid-clearance tests (%)	Growth increment (g.)	
		Fœtus	Uterus
Normals	0	..	..
12	8	13	60
13–16	26	94	200
17–20	32	208	180
21–24	33	314	170
25–28	37	415	100
29–32	30	635	..
33–36	47	698	..
37–40	68	1027	..
Full term	36	..	..
43–45	33	..	..
Twins	100	..	..
Megaloblastic anæmia	100	..	..

Fœtal growth-rate after Streeter (1920).
Uterine growth-rate (approx.) after Gillespie (1950).

The peak concentration in 10 patients with megaloblastic anæmia in pregnancy who were tested after the anæmia had been treated with folic acid was 10–60 µmg. per ml. (mean 37±6). This level was significantly lower than that found in pregnant controls (P=0·05).

The absorption of folic acid was retested in 2 patients with megaloblastic anæmia of pregnancy 3 months after delivery. In both the absorption of folic acid had returned to normal; the peak serum-folic-acid concentrations were

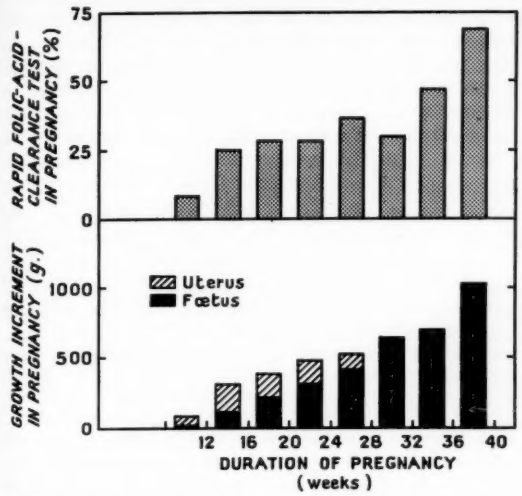

Fig. 5—Incidence of abnormal folic-acid-clearance tests in pregnancy compared with the rate of growth of the fœtus (Streeter 1920) and uterus (Gillespie 1950).

23 and 33 μmg. per ml. during pregnancy, and 72 and 72 μmg. per ml., respectively, after pregnancy.

Discussion

INTERPRETATION OF THE FOLIC-ACID-CLEARANCE TEST

The rate of clearance from the plasma of small doses of folic acid appears to depend on the degree of " saturation " of the tissues for this vitamin, for very little of an intravenously injected dose is excreted in the urine. If the tissues of normal subjects are " saturated " with folic acid by giving large doses by mouth 24 hours before the test, the rate of clearance is slower than in normal healthy subjects not treated in this way (Chanarin et al. 1958c). On the other hand, an abnormally rapid clearance suggests that the tissues are more " unsaturated " for folic acid than the tissues of normal subjects, and this has been interpreted as indicating that these tissues are depleted of folic acid (Chanarin et al. 1958c).

Folic-acid deficiency presumably occurs if the demand for the vitamin exceeds the intake. A moderate increase in demand for folic acid could perhaps be met without depleting the body of folic acid if the diet is good. If the demand for folic acid, however, exceeds the amount absorbed, the tissues will be depleted, and under these circumstances the rate of clearance of intravenously injected folic acid will be more rapid than in normal subjects.

A rapid clearance of folic acid, and of folinic acid (Spray and Witts 1953), has been found in conditions known to be associated with the development of megaloblastic anæmia requiring treatment with folic acid and in which Broquist (1956), Luhby (1957), and Luhby et al. (1958) demonstrated the excretion of formimino-glutamic acid in the urine. The metabolite accumulates and is excreted in the urine in folic-acid-deficient animals (Silverman et al. 1952).

FOLIC-ACID DEFICIENCY IN PREGNANCY

The dose of folic acid injected in the clearance test was adjusted for the increased body-weight throughout pregnancy, and, although changes of plasma-volume may affect the initial 3-minute serum levels, these are unlikely to influence the subsequent rate of removal of injected folic acid from the plasma. The rapid clearance of folic acid from the plasma in pregnant women therefore indicates an increased demand for folic acid in pregnancy and presumably a conditioned folic-acid deficiency.

The close correlation between the growth-rate of the fœtus and the incidence of abnormal folic-acid-clearance tests (fig. 5) suggests that an important factor causing this deficiency in pregnancy is the fœtal requirement for folic acid. The very much higher incidence of abnormal tests in twin pregnancy supports this view. However, the results of the folic-acid-absorption test suggest that impaired absorption of folic acid may also play a part in producing the deficiency. The serum-folic-acid levels in pregnant women after an oral dose of the vitamin (fig. 6) were often lower than in healthy subjects and were sometimes as low as those seen in patients with intestinal malabsorption syndrome (Chanarin et al. 1958a). These lower serum-folic-acid levels could be due to delayed gastric emptying if this is present in pregnancy. However, as the peak folic-acid levels were reached at the same times in the pregnant subjects and in healthy controls this is unlikely to be the explanation, and the most probable cause of these lower levels is impaired absorption of the vitamin.

Alteration in gastrointestinal functions has been frequently reported in pregnancy. Thus there may be a reduction in volume and acidity of gastric secretion (Murray et al. 1957), and possibly in the secretion of intrinsic factor (Strauss and Castle 1933); the glucose-tolerance curve is flat in about 40% of pregnant patients (Basil-Jones 1949, Lund and Weese 1953); and the absorption of fat may also be impaired (Davis and Brown

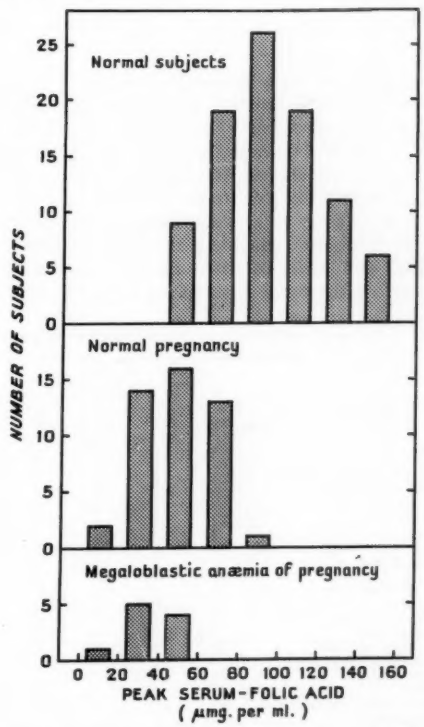

Fig. 6—Peak serum concentration of folic acid, after an oral dose of 40 μg. per kg., in 90 normal subjects, 45 pregnant women, and 10 patients with treated megaloblastic anæmia of pregnancy.

R2

1953, Giles and Shuttleworth 1958). Moderate depression of folic-acid absorption may be of little importance when the requirement for folic acid is normal but may precipitate deficiency when the requirement for this vitamin is increased as in pregnancy.

Deficiency at Term

The clearance of folic acid was most rapid in the last 4 weeks of pregnancy, and was significantly slower in patients at term. It would seem that at full term maternal tissues are less depleted with respect to folic acid, presumably owing to a decline in the fœtal demand.

MEGALOBLASTIC ANÆMIA OF PREGNANCY AND THE PUERPERIUM

Megaloblastic anæmia in pregnancy does not respond adequately to treatment with vitamin B_{12} (Thompson and Ungley 1951). All patients respond completely to treatment with folic acid (Moore et al. 1945). Megaloblastic anæmia in pregnancy therefore appears to be due to interference with folic-acid metabolism or to deficiency of folic acid. The evidence in this paper suggests that patients with megaloblastic anæmia of pregnancy are folic-acid deficient. This is supported by the observation of Luhby (1957), who demonstrated that a patient with megaloblastic anæmia of pregnancy excreted large amounts of formimino-glutamic acid in her urine.

The time of onset of the anæmia and the high incidence in twin pregnancy suggests that the severe folic-acid deficiency in megaloblastic anæmia of pregnancy is also the result of increased fœtal demand. But in these patients defective absorption of folic acid and poor dietary intake may also contribute to the pathogenesis of this anæmia.

Time of Onset

Although more than half of the 318 cases of megaloblastic anæmia of pregnancy and the puerperium drawn from the literature (table v) were diagnosed in the puerperium, the work of Giles and Shuttleworth (1958) suggests that the great majority can be diagnosed during late pregnancy by examining the sternal marrow. On the other hand, only 12 cases (4%) were diagnosed before the 30th week. Megaloblastic anæmia is therefore a disease of late pregnancy and develops when the rate of fœtal growth and therefore the fœtal demand for folic acid is greatest, and when the rate of clearance of folic acid from the plasma is most rapid (tables III and IV).

On this hypothesis the pronounced tendency for the anæmia to remit spontaneously in the puerperium can be explained by the cessation of fœtal demand for folic acid and by a return of normal gastrointestinal function after delivery.

Incidence in Twin Pregnancy

Megaloblastic anæmia is common in patients with twin pregnancy (Girdwood 1956, Scott 1957, Thompson 1957, Giles and Shuttleworth 1958), being 8 times more frequent than in single pregnancy (table v). There is therefore a very high incidence of both folic-acid deficiency and megaloblastic anæmia in patients with twin pregnancy. Both are presumably the result of greater demand for folic acid by two fœtuses.

Absorption of Folic Acid

Patients with megaloblastic anæmia of pregnancy do not appear to absorb folic acid as well as normal pregnant controls (fig. 6). Megaloblastic anæmia is therefore more likely to appear in those patients whose intestinal function is most affected in pregnancy.

Diet

Megaloblastic anæmia in pregnancy can be prevented if enough folic acid is present in the diet, and Lowenstein et al. (1955) found that megaloblastic anæmia disappeared when a vitamin supplement which included 1 mg. of folic acid was given 3 times a day to their antenatal patients.

The exact requirements for folic acid in healthy subjects are unknown, so the relationship of diet to the development of megaloblastic anæmia in pregnancy is uncertain. Nevertheless, patients who develop megaloblastic anæmia in pregnancy often take an inadequate diet (Thompson and Ungley 1951, Giles and Shuttleworth 1958).

Both Thompson (1957) and Forshaw (1957) noted a higher incidence of megaloblastic anæmia in late winter in this country and suggested that this was due to the relative scarcity of green vegetables, which may be an important source of folic acid. A seasonal incidence, however, was not apparent in the patients reported by Giles and Shuttleworth (1958) nor in 120 patients studied by Mollin et al. (1959).

The very much higher incidence of severe megaloblastic anæmia in India and parts of Africa and its relative infrequency in Australia and North America may be due, at least in part, to differences in dietary intake of folic acid.

Folic-acid Deficiency and Onset

The results in this paper suggest that folic-acid deficiency may develop in normal pregnancy and that megaloblastic anæmia develops in those patients in whom the deficiency is most severe. However, although megaloblastic anæmia was associated with the most severe degrees of folic-acid deficiency as assessed by the folic acid clearance test, the clearance was often as rapid in patients with twin pregnancy in whom there was no evidence of megaloblastic anæmia. This suggests that some other factor may be required to precipitate megaloblastic erythropoiesis in these patients when folic-acid deficiency is already present. The nature of such factor or factors is unknown.

TABLE V—TIME OF DIAGNOSIS OF MEGALOBLASTIC ANÆMIA IN PREGNANCY AND INCIDENCE OF TWIN PREGNANCY

Authors	No. of cases	Diagnosis at			Twins
		20–30 weeks	31–40 weeks	Post-natal	
Adams (1956)	10	0	5	5	..
Agüero and Layrisse (1958)	20	0	11	9	..
Badenoch et al. (1955)	9	0	4	5	1
Buckle and Shaw (1957)	5	1	4	0	..
Clark (1952)	18	2	7	9	..
Clarke and Essig (1954)	3	0	3	0	..
Davidson et al. (1942)	16	0	2	14	..
Day et al. (1949)	1	1	0	0	..
Forshaw et al. (1957)	21	0	13	8	..
Giles and Shuttleworth (1958)	90	5	57	28	7
Hollingsworth and Adams (1955)	2	0	1	1	..
Israëls and Da Cunha (1952)	6	1	4	1	1
Killander (1958)	3	0	2	1	..
Lowenstein et al. (1955)	18	0	9	9	1
Miller and Studdert (1942)	23	0	0	23	..
Moore et al. (1955)	17	0	5	12	..
Scott (1957)	(19)	..	..	..	4
Thompson and Ungley (1951)	45	0	6	39	..
Thompson (1957)	(100)	..	..	..	10
This study	11	2	6	3	2
Total	318	12	139	167	..
Twins	253	..	..	..	26

Summary

The incidence and severity of folic-acid deficiency was studied in a large group of pregnant subjects and healthy

controls by following the rate of clearance from the plasma of a small intravenous dose of folic acid. The absorption of folic acid was studied by following the rise in the serum-folic-acid level after a small oral dose of the vitamin.

The rate of clearance of folic acid from the plasma was increased in two-thirds of pregnant subjects in late pregnancy, and in all patients with twin pregnancy. It is concluded that the increased rate of clearance is due to folic-acid deficiency. This deficiency appears likely to be due mainly to the fœtal requirement for folic acid exceeding the dietary intake, but impaired absorption of this vitamin during pregnancy may also play a part.

The rate of clearances of folic acid from the plasma was even more rapid in patients with megaloblastic anæmia of pregnancy. The high incidence of this anæmia in twin pregnancy and its onset in late pregnancy suggests that the factors producing folic-acid deficiency in normal pregnancy are responsible for the more severe folic-acid deficiency in patients with megaloblastic anæmia. Since the absorption of folic acid appeared to be most impaired in the patients with megaloblastic anæmia this may contribute to the development of the more severe grade of folic-acid deficiency found in these patients. The dietary intake of folic acid may also be important.

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LOBECTOMY FOR BRONCHIAL CARCINOMA

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FOR some years there has been a trend towards conservatism in the surgical treatment of bronchial carcinoma. This trend has gained ground to such an extent that Robinson et al. (1956) were able to show that no less than 92·8% of American surgeons were guided by the principle "lobectomy where possible". More recently this policy has been carried to its logical conclusion by Johnston and Jones (1959). They described a technique of "sleeve resection" to enable lobectomy to be performed in patients in whom hitherto pneumonectomy would have been thought essential because of the local extent of the disease.

A series of 264 lobectomies for carcinoma recorded three years ago (Belcher 1956) was based on the experience of fifteen British thoracic surgeons who had followed the principle of "policy lobectomy" for at least five years. These short-term results were thought to justify the procedure; but 156 patients had been followed up for only two years, and only 18 for five years.

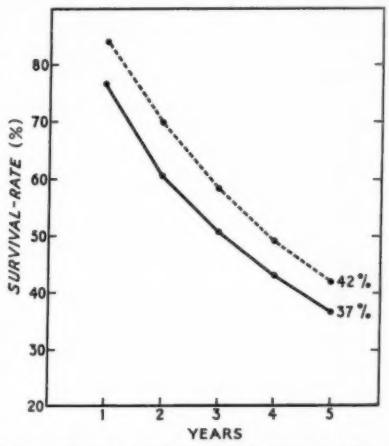

Fig. 1—Annual survival-rate. Interrupted line shows rate excluding deaths from causes other than bronchial carcinoma.

This paper describes a further study of the same 264 cases, all of which have been followed for five years or more.

Results

Of the 264 patients, 12 died as direct result of their operation: these have been excluded from the analysis. 6 of the remaining 252 have been lost sight of; these also have been excluded. This leaves 246 patients for study.

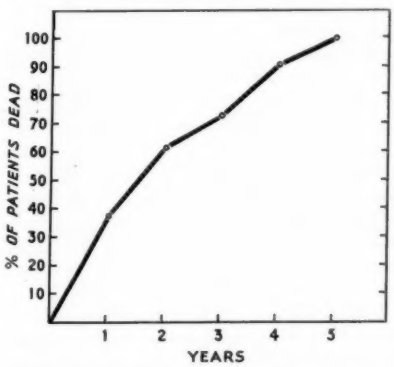

Fig. 2—Proportion of patients dead, by years up to five years.

Of these patients, 107 were already dead at the time of the original survey. 62 have died since

TABLE I—CAUSES OF DEATH

Cause	No.
Operative mortality	12 (7%)
General metastases	83 (45%)
Local metastases	47 (26%)
Other	30 (18%)
Unknown	9 (5%)

that time. 14 patients died more than five years after operation; thus 91 (37%) were alive at five years. This figure includes those patients who died from causes other than bronchial carcinoma. There were 30 such patients (12%), and if these are excluded from the analysis the five-year-survival rate is 42% (fig. 1).

Of the patients who have died since operation, 61% did so within two years. Thereafter the decline in the number of survivors was steady up to, and even beyond, five years (fig. 2). This gradual but steady fall contrasts with that seen in patients treated by pneumonectomy: in these patients up to 80% of those who died within the first five years after operation had done so in the first two years (Bignall and Moon 1955).

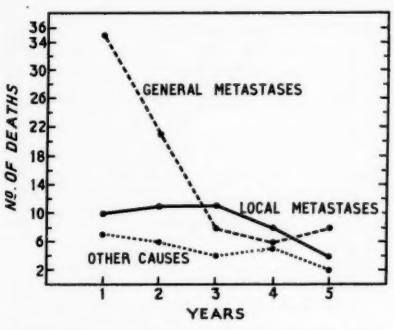

Fig. 3—Number of deaths, by causes, up to five years.

In this series the proportion of patients who died from general metastases was smaller than in those cases of bronchial carcinoma where pneumonectomy is necessary. This is due to the fact that, where lobectomy was possible, the case was encountered earlier in the development of the disease. As a high proportion of deaths due to general metastases occur in the first two years, the lower incidence of deaths in this period after lobectomy can be accounted for by this lower incidence of general metastases.

Cause of Death

The cause of death was known with reasonable certainty in all but 9 patients, although the distinction between local and general metastases was sometimes difficult (table I). At least 77% died of their original disease.

The number of deaths each year from each cause is shown in fig. 3. The number who died from general metastases was high in the first two years, but thereafter this number followed the number of deaths from the other two causes closely. This is because in many patients unrecognised secondaries were present at the time of the first operation, and in the majority these were responsible for death within the first two years.

The number who died of local metastases remained fairly constant each year, falling off a little towards the fifth year. The same was true of the patients who died of causes other than carcinoma. A third of these deaths were due to coronary thrombosis, and a third to respiratory failure.

Relation of Histological Findings and Glandular Metastases to Results

The previous analysis (Belcher 1956) showed that, although the patients with adenocarcinomata had the best prognosis, there was little difference between those with oat-cell or with squamous carcinoma. (This finding was also noted by Davis et al. 1958). These two points have been emphasised by the longer follow-up (fig. 4). The five-year-survival rate of 46 patients with adenocarcinoma was 53%, of 158 with squamous carcinoma 32%, and of 42 with oat-cell carcinoma 37%.

TABLE II—FIVE-YEAR-SURVIVAL RATE ACCORDING TO GLANDULAR INVOLVEMENT

Type of carcinoma	Proportion (%) with glands involved	Five-year survival (%)	
		With glands	Without glands
Adenocarcinoma	35	65	35
Oat-cell	30	43	23
Squamous	29	37	21

The presence of glandular metastases has been shown to be a dominant factor influencing prognosis in carcinoma of the bronchus. The figures in this series are no exception to this rule (fig. 5). Of 183 patients in whom the mediastinal glands were thought to be free of tumour, 43% were alive at five years, whereas of the 63 in whom glands were invaded only 23% survived that time.

The difference in expectation of life between the three different cell types cannot be accounted for by a different incidence of glandular involvement (table II). In fact the incidence in adenocarcinoma was the highest, and in squamous carcinoma the lowest—the exact opposite of the survival-rates. The difference in prognosis must be inherent in the tumour.

Thus the five-year-survival rate of patients with adenocarcinoma without glandular metastases was 65%, whereas, at the other end of the scale, the rate in patients

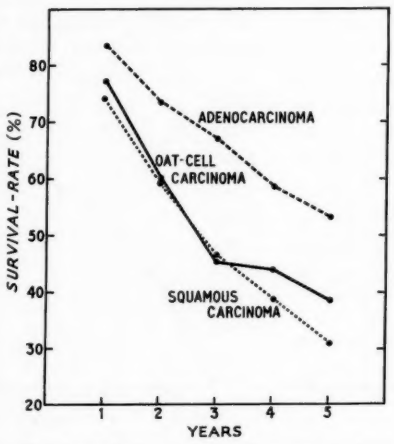

Fig. 4—Influence of cell type on survival-rate.

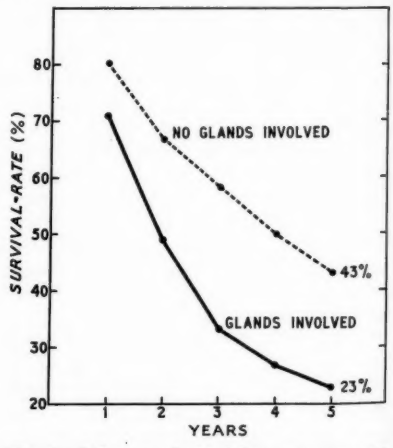

Fig. 5—Influence of glandular metastases on survival.

TABLE III—FIVE-YEAR-SURVIVAL RATE RELATED TO SITE OF CARCINOMA

Site	Alive	Dead	Five-year survival (%)	
Rt upper lobe	19	39	33	31
Lt upper lobe	23	53	39	
Rt lower lobe	30	41	42	44
Lt lower lobe	19	22	46	

with squamous carcinoma with glandular involvement was 21%.

Site and Type of Tumour

In the original paper (Belcher 1956) it was shown that the side of the lesion had little influence on the prognosis, and that in lower-lobe tumours it was a little better than in upper-lobe tumours.

After the longer follow-up, the difference between upper and lower lobe tumours has become much more apparent; this must be a significant difference (table III).

Secondly, it was shown that there was little difference in the prognosis between circumscribed and uncircumscribed tumours. This was still true after five years.

It was also shown that the prognosis was worse in those patients in whom the operation was considered to be only palliative. This was of course anticipated, but the difference between the "policy" and the "palliative"

TABLE IV—POSSIBLE AND ACTUAL SURVIVORS

Years	Possible survivors	Actual survivors	
		No.	% *
6	183	40	22
7	106	25	23
8 and over	42	9	21

* $\frac{\text{Actual survivors}}{\text{Possible survivors}} \times 100$

The number of patients available for study after eight years was too small to be informative.

groups was not as great as had been expected (39% as against 28%).

Patients Operated On More than Five Years Ago

A decreasing number of patients was available for study after the five-year period. The survival-rate of these is shown in table IV as $\frac{\text{actual survival}}{\text{possible survival}} \times 100$. The increase in the rate is due to the smaller number of patients at the end of the series. After eight years this number is too small for analysis.

In the five-to-ten-year period there were 14 deaths. 5 patients died from general metastases, 3 from local metastases, and 6 from other causes. The pattern of mortality is thus the same after five years as it was before that time, and metastases continue to appear both locally and generally at much the same rate.

Carcinoma in Residual Lung Tissue

At the time of the original survey, 12 patients had developed carcinoma either in the residual lobe on the side of the operation, or in the other lung. Since that time a further 7 such cases have occurred—7·5% of the whole series. No particular cell type was associated with this occurrence.

In 8 cases the recurrences were obviously part of a general metastatic process; but, of the remaining 11, 9 occurred on the side opposite to the original resection, and 1 of those occurring on the opposite side was thought to be a new primary tumour. Although all these cases have been included under the heading of "local metastases", these solitary lesions may all have been new primary tumours. 3 of these tumours were treated by a second resection: 1 patient died at the operation, but the other 2 are alive.

Thus the impressions from the short follow-up of a large series have been largely borne out by the five-year follow-up. The only difference is that the better prognosis of lower-lobe tumours has become more apparent.

Discussion

Since 1956 important information about the local spread of bronchial carcinoma has become available, and hence a more rational approach to its surgical treatment has become possible.

Nohl (1956) has shown that the lymphatic pathways from individual lobes to the mediastinum are constant. Thus it is perfectly feasible to attempt radical lobectomy (Boyd et al. 1954). The ideal cancer operation should include removal of the lobe containing the tumour and the glands to which this lobe normally drains. Pneumonectomy is not always essential to achieve this end.

Nohl (1954) also confirmed the sinister significance, not only of mediastinal metastases, but also of venous involvement, in the prognosis of bronchial carcinoma.

Direct spread of pulmonary carcinoma either in the bronchus or in the peribronchial lymphatics should be considered in planning a radical operation. Cotton (1959) has shown that the spread in the bronchial wall itself extends beyond the extrabronchial mass in only 12% of cases, and then only to a maximum of $\frac{3}{4}$ in. The spread in the wall seldom extends nearly as far as the intrabronchial malignant polyps commonly seen in bronchial carcinoma. He has also shown that the incidence of peribronchial spread is not as great as has been thought, occurring in only 6% of cases, and that it occurs only in association with heavy involvement of mediastinal lymph-nodes with metastases.

These findings again show that lobectomy has a sound pathological basis, except where the tumour involves the orifice of the affected bronchus.

Resection of a ring of bronchus followed by end-to-end anastomosis is a safe procedure, and can be carried out where the involvement of the bronchial wall by upper-lobe tumours would have hitherto necessitated removal of the undiseased lower lobe (Johnston and Jones 1959).

The five-year-survival rate of 37% compares favourably with that of any published series. Bignall and Moon (1955) gave a figure of 33% in a mixed group of patients treated by either pneumonectomy or lobectomy; Burford et al. (1958) gave a rate of 22%; Johnson et al. (1958) gave a rate of 27%, and they remained unconvinced that the results of radical pneumonectomy are superior to those of more conservative operations. (Both these series included operative mortality.) On the other hand, Robinson et al. (1956) had a three-year-survival rate of 71% among 21 patients treated by lobectomy, as against 16% in 123 patients treated by pneumonectomy during the same period.

The results of lobectomy must be expected to be superior to those of pneumonectomy as the tumours must be earlier in their course; nevertheless the comparison of the two operations seems to justify the policy of conservatism.

Perhaps the most important finding in the longer follow-up has been the difference in prognosis between the upper and the lower lobe tumours. Aylwin (1951) pointed to the risk of bloodborne metastases due to tumour emboli caused by manipulation of the tumour. He recommended ligature of the vein as a first step in all

resections for carcinoma. It was thought possible that a technical difference between the sequence in which the major structures in the hilum were dealt with might account for the difference in prognosis. All the surgeons concerned were asked to give details of their technique, but, although this varied widely, little difference in their results was found whether the vein was tied early or late in the procedure. Perhaps therefore the difference is due to the greater ease with which the glands draining the lower lobe can be removed at lobectomy.

If lobectomy were an inadequate operation, the tendency towards conservatism would have been reflected in a lower overall survival-rate. This has not been shown. It seems, therefore, that on both pathological and statistical grounds the present popularity of the more conservative resection in the treatment of bronchial carcinoma is justified.

Summary

264 cases of lobectomy for bronchial carcinoma more than five years ago have been analysed.

Those patients who died at operation or who have been lost have been excluded, leaving 246.

The five-year-survival rate was 37%. Excluding the 30 patients who died from other causes it was 41%.

The survival-rate for adenocarcinoma was 53%, for oat-cell carcinoma 37%, and for squamous carcinoma 32%. This difference was not due to the different incidence of glandular invasion.

The five-year-survival rate for patients with glandular involvement was 23%, compared with 43% in those in whom the glands were tumour-free.

The survival-rate was significantly better for lower-lobe tumours (44% as against 31%).

14 patients died between five and ten years after lobectomy.

19 patients (7·5%) developed carcinoma in the residual lung. In 11 it was thought possible that these might be new primary tumours.

The present trend towards conservatism in the surgical treatment of bronchial carcinoma is justified.

Renewed gratitude is due to my colleagues: Mr. K. Mullard, Mr. G. Cruikshank, Mr. C. A. Jackson, Mr. M. Bates, Mr. A. M. Macarthur, Mr. R. Abbey Smith, Mr. E. F. Chin, Mr. M. M. Brown, Mr. K. Harrison, Mr. I. M. Hill, Mr. B. P. Moore, Mr. L. Bromley, and Mr. H. R. S. Harley. Their great cooperation and thorough follow-up has made this report possible.

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". . . Though the Welfare State is largely the product of compassion for ordinary folk, for the common man as the democratic cliché has it, it will be the exceptional men . . . who will ultimately justify its existence. For individuals, as for nations, doing well in life and doing something in life are contradictory aims. The real test for the Welfare State will be whether it has been able to merge the two ends, so far as they can be merged."—NIRAD C. CHAUDHURI, *A Passage to England*, p. 214. London, 1959.

DENTAL EXTRACTIONS IN PATIENTS WITH HÆMOPHILIA AND CHRISTMAS DISEASE

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THE extraction of teeth from the hæmophilic patient has in the past been carried out with great reluctance on the part both of patient and dental surgeon. A better understanding of the coagulation defects in hæmophilia and allied disorders has led, however, to more effective measures for the control of hæmorrhage; and these have revolutionised the management of such cases.

Treatment is both local and general. The former depends on the use of acrylic splints made to fit each patient individually (Matheson 1949): the latter consists of blood or antihæmophilic globulin (A.H.G.) transfusions. These measures enabled Orr and Douglas (1957) to control the bleeding within seven days in most of their 9 hæmophilic patients and 1 case of Christmas disease. These workers did not recommend the extraction of more than four teeth at a time; but, using specially constructed splints and larger volumes of fresh plasma, Wishart et al. (1957) removed up to sixteen at one sitting.

In this paper we shall describe the steps we take during the extraction of teeth in patients with hæmophilia and Christmas disease. We shall also consider the effect of different factors on postoperative bleeding.

Management of Patients

During the past seven years we have extracted teeth from 49 patients with classical hæmophilia and 9 with Christmas disease. 81 separate dental operations were performed, involving the removal of one to twenty-five teeth at one session. The age-distribution of the patients is shown in table I. It will be seen that dental operations are carried out more often in the young.

TABLE I—AGE-DISTRIBUTION OF PATIENTS

Age (years)	No. of patients
Under 15	20
15–25	16
26–35	9
over 35	13
	58

The management of these patients is now relatively simple. We have taken into consideration that many of them need frequent hospital attention for hæmorrhagic episodes, and that it is therefore desirable to reduce as far as possible the number and length of their admissions for dental extractions. Storage, moreover, has an adverse effect on A.H.G. (Brinkhous et al. 1956) and Christmas factor (Nour-Eldin and Wilkinson 1958a); and both factors are rapidly removed from the circulation (Lang-

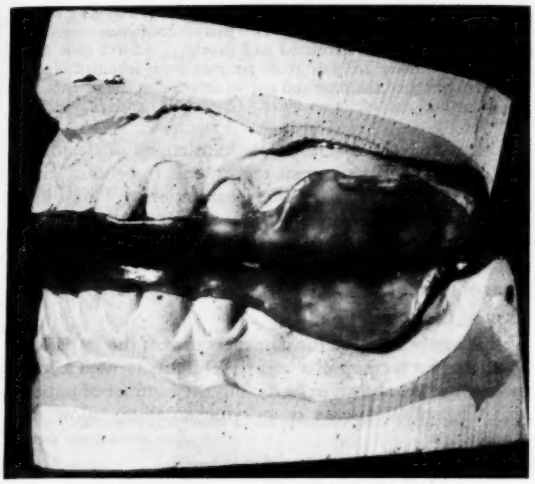

Fig. 1—Acrylic splint on stone model.

dell et al. 1955, Nour-Eldin 1958, Nour-Eldin and Wilkinson 1958a).

Preoperative Procedures

New patients with a history suggestive of a bleeding diathesis were investigated in this clinic for hæmophilia or Christmas disease. Full clinical and radiological examinations of the teeth and jaws, especially for unsaveable carious, unerupted, or impacted teeth, were carried out at the same time. In children, consideration was given to overcrowding of the teeth, causing malocclusion; and this was taken into account when deciding the plan of treatment.

If operative treatment was necessary, as much as possible of the preoperative preparation and treatment was carried out as an outpatient. Usually the splint, the most important preoperative measure, was also prepared before admission (figs. 1–3).

Alginate impressions are taken of the upper and lower jaws. On the stone models obtained from these impressions, the splints are designed and made in clear acrylic. The design necessarily varies according to the position and number of teeth to be extracted. Fig. 1 shows clear acrylic splints on articulated stone models designed for controlling hæmorrhage after removal of the upper and lower molar teeth. Fig. 2 illustrates a lower splint in position immediately after the removal of the lower left first and second molars. The condition of these sockets when hæmostasis was achieved on the sixth day can be seen in fig. 3.

The patients were admitted to hospital at least a day before extractions so that the adequacy of the prepared splints could be checked. Since many hæmophilic patients in the past have suffered from faulty dental management and are inclined to be more than usually anxious, the opportunity was also taken to allay their natural apprehension.

Oral antibiotics were started a few hours before the extractions and continued while the splint was being worn.

Transfusions

The control of hæmorrhage has been ensured by the liberal use of fresh blood—that is blood given within four hours of being collected. The first transfusion was invariably whole blood; but thereafter if the hæmoglobin was 13·5 g. per 100 ml. (92%) or more, plasma separated by centrifugation at 1500 r.p.m. for thirty minutes was given. Only one pint of fresh blood in twenty-four hours was given, but when the hæmoglobin fell sharply, the deficit was made up with either stored blood or packed red cells. If possible the initial transfusion of fresh blood was given in the morning, and the teeth were extracted as soon as this was completed. The patient was always taken in his bed from the ward to the dental department and the extractions were carried out in his bed, not in the dental chair.

More fresh blood was given on the first and second post-extraction days, and further transfusions were planned according to progress. Most patients needed supplementary blood between the fourth and seventh day, and a few needed blood up to ten days after the extraction.

In patients with Christmas disease we have tried to control the hæmorrhage with up to five-day-old blood or plasma only; but, because in practice this did not always prove satisfactory, we now use fresh whole blood or fresh plasma. Nevertheless, for controlling the oozing that sometimes remains troublesome after the fifth day we have found five-day-old stored plasma adequate.

Anæsthesia

Local anæsthesia was the method of choice, general anæsthesia being reserved for children and very apprehensive adults. The local anæsthetic solution we most use is 2% ' Lignocaine ' with 1/80,000 adrenaline. We have found that, when teeth have to be removed from more than one quadrant, the local anæsthetic can be given to all regions at the same time with efficiency and safety.

No injection hæmatoma was produced in any of our patients even when four quadrants were involved.

In the induction of general anæsthesia special care is needed to avoid injuring the airway by the endotracheal tube; consequently, this is best introduced orally, even though it limits the operative field.

Extractions

The teeth were removed with the least possible trauma, the sockets were digitally compressed, and the acrylic splints were inserted. Occasionally roots had to be exposed surgically. The mucosa was *never sutured* because of the risk of subsequent bleeding from the suture holes and of the hæmatoma causing respiratory obstruction. Thrombin solution was instilled into the sockets in the earlier patients, but this did not appear to have any advantage.

Fig. 2—Splint in position.

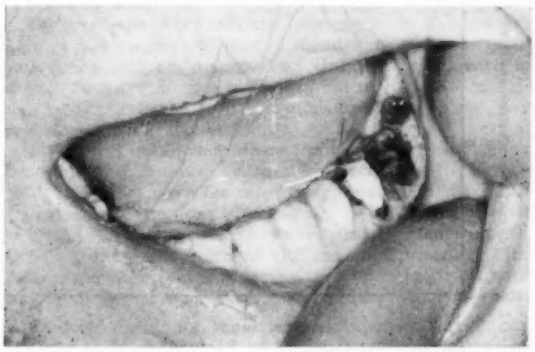

Fig. 3—Sockets after removal of splint on the sixth postoperative day.

Postoperative Management

To reduce venous pressure the patient was sent back to the ward with his head raised on pillows, and he was kept in bed until the bleeding stopped. A jaw support or harness was applied (fig. 4) to keep the splinted jaws in occlusion and so to maintain the splints in correct position. This is extremely important, because if the splints are slightly displaced, hæmorrhage is likely to displace them still further, and swelling of the alveolar tissues may make it difficult to replace them. The jaw support serves to remind the patient to limit his talking and thus rest the mouth.

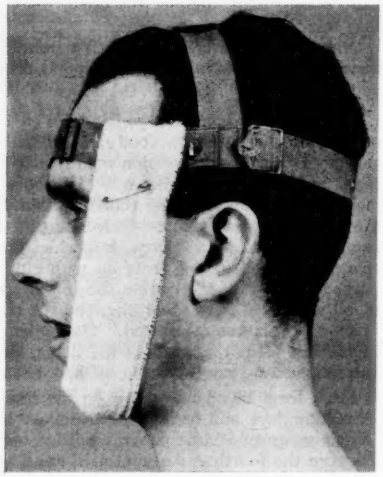

Fig. 4—Jaw support in position after teeth extraction.

During the postoperative period patients received a 2500-calorie, high-protein fluid diet; this was given through a polythene tube when necessary. The mouth was cleaned daily with sodium-bicarbonate solution to lessen fœtor oris. The splints were usually removed twenty-four hours after the oozing of blood from the sockets had ceased.

Observations

Effect of Number of Teeth Extracted

We have been able to remove at one operation up to twenty-five teeth. The extraction of one tooth seems to need the same amount of preparation and to keep the patient in hospital for as long as the removal of many teeth. Nevertheless, we have examined the effect of the number of teeth extracted on the severity and duration of the subsequent hæmorrhage.

Fig. 5 shows the frequency of single and multiple extractions in the group as a whole. In fig. 6 the group has been divided into two classes—those who have had less than four, and those who have had four or more permanent teeth removed.

Calculations were based on 55 observations. The total correlation coefficient between the number of teeth extracted (x) and the days of bleeding (y) was calculated for the whole group, and gave a value of $r_{xy}=0{\cdot}037$ (not significant). The partial coefficient to exclude age (z) effect was also calculated and gave $r_{xy.z}=0{\cdot}072$ (not significant). In a similar analysis of 20 patients from whom deciduous teeth were removed the total and partial correlation coefficients gave the following values: $r_{xy}=0{\cdot}618$ ($P<0{\cdot}01$), and $r_{xy.z}=0{\cdot}627$ ($P<0{\cdot}01$).

It thus appears that multiple extractions of deciduous teeth, but not of permanent teeth, tend to produce more prolonged bleeding than single extractions. This difference is most marked between the fourth and the seventh postextraction day (fig. 7) and may be due to the different behaviour of granulation tissue in young and older hæmophilics.

Effect of Clotting Defect

Differences between the clinical course of the 49 patients with classical hæmophilia and the 9 patients with Christmas disease are shown in fig. 8; but the number of patients with Christmas disease is still too small to allow firm conclusions.

Effect of Age and of Bridge Anticoagulant

The belief is widely held by hæmophilic patients that hæmorrhagic manifestations become less severe and less frequent with increasing age. We therefore examined the relationship between the duration of the postextraction bleeding and the age of the patients (2–77 years, table I).

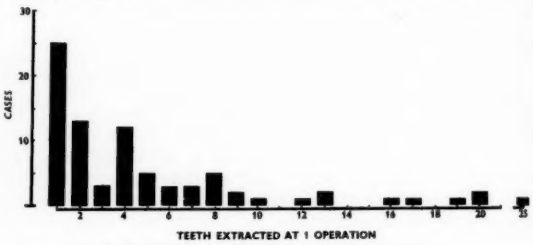

Fig. 5—Frequency of multiple teeth extractions.

The total correlation was $r_{yz}=-0{\cdot}235$ ($0{\cdot}1>P>0{\cdot}05$). Partial correlation (excluding variation in x, the number of teeth) was $r_{yz.x}=-0{\cdot}242$ ($0{\cdot}1>P>0{\cdot}05$), where y is the number of days of bleeding and z the patient's age. A similar value of the partial correlation coefficient based on a greater number of observations (75) would have been significant at the 5% level, but the result suggests a negative correlation between duration of bleeding and age.

Though our observations would thus appear to support the opinion held by many patients, a third variable must be taken into account. Multiple extractions are more likely to be required in older patients; and, since severe

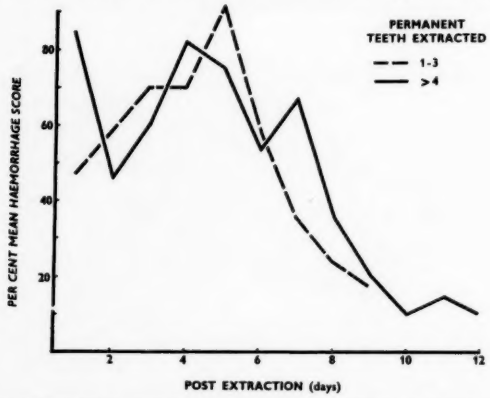

Fig. 6—Effect of extraction of different numbers of permanent teeth on postoperative bleeding.

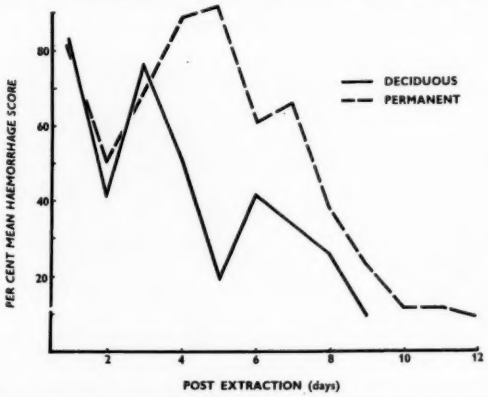

Fig. 7—Bleeding trend after removal of deciduous and permanent teeth.

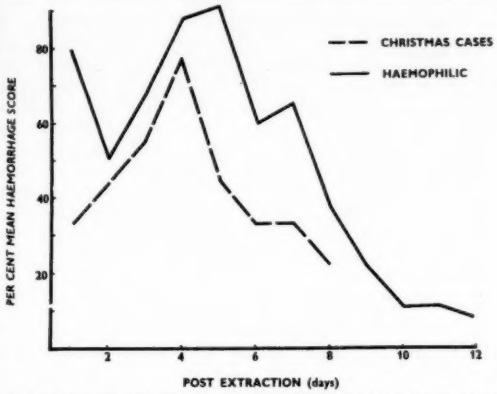

Fig. 8—Hæmorrhagic trend in hæmophilia and Christmas disease after teeth extraction.

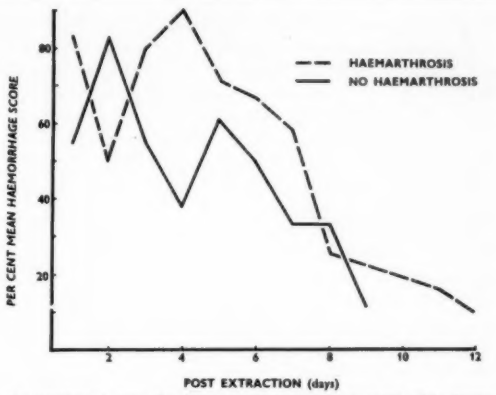

Fig. 9—Postoperative bleeding trend in patients with high (hæmarthrosis) and low (no hæmarthrosis) concentration of Bridge anticoagulant.

hæmophilia reduces life expectancy, they may include a higher proportion of the less severe cases. To evaluate the effect of this variable, we examined the relationship between the hæmorrhage after extraction and the severity of the illness.

Our clinical assessment was based on the presence or absence of a hæmorrhagic manifestation—for example spontaneous hæmarthrosis—which is taken as an indication of the presence of Bridge anticoagulant (Nour-Eldin and Wilkinson, 1958b and c). For the postextraction bleeding we drew up the following arbitrary scale:

Postextraction bleeding = 2
Postextraction oozing = 1
No hæmorrhage = 0

From this a score was worked out for each patient, as shown in table II

TABLE II—SCORING OF POSTEXTRACTION BLEEDING

Patient	Days after extraction										
	1	2	3	4	5	6	7	8	9	10	11
A	2	1	0	1	1	0	1	0	0	0	0
B	1	2	1	0	2	0	1	0	1	0	0
C	1	0	2	1	1	0	1	0	1	1	0
Score	4	3	3	2	4	0	3	0	2	1	0

Fig. 9 shows the mean hæmorrhage score against the number of days of postextraction bleeding in the two groups—i.e., the 31 patients with high concentration of Bridge anticoagulant, and the 18 mild cases with low concentration. The graphs showing the relation of the bleeding score to the postoperative day appear to differ: in particular, the two groups show opposite trends on the first and second day.

Serum and Plasma in the Treatment of Christmas Disease

Following the observation of Nour-Eldin and Wilkinson (1958a) that serum does not influence the generation of plasma-thromboplastin, we carried out a clinical trial with this agent.

The patient, aged 8, was given 500 ml. serum before the extraction of four teeth. The operation was followed by severe hæmorrhage, reducing the hæmoglobin from 12·7 g. (86%) to 10·1 g. (68%) per 100 ml. The patient was given a further injection of 200 ml. serum, but the bleeding continued. It ceased as soon as 540 ml. stored blood (less than five days old) was administered.

Complications

The patients must be watched for the postextraction complications.

Traumatic hæmorrhage may arise from abrasions by splints: it occurred in 2 of our earliest cases. It can be avoided by taking great care in designing well-fitting splints. Hæmatomata may also result from too tightly applied splints if hæmatological control by blood-transfusion is not fully maintained. This was seen in 1 patient who responded promptly to easing of the splint and to fresh blood. The untimely removal of splints by very young patients can be prevented by wrapping the child's arms in loose cardboard.

Loss of sensation in the area supplied by the right inferior dental nerve was noted in a boy aged 16 the day after extraction. It was apparently due to a hæmorrhage in the inferior dental canal.

Zinc oxide-' Eugenol ' cement paste as a lining to the splint must be used with care. Excess, especially if it flows into the interdental spaces of the remaining teeth which may themselves be affected by periodontal disease, may cause difficulty in removing the splint. We no longer use this paste; but should it be necessary, application should be strictly limited to the region of the extractions.

Discussion

Both therapeutic and prophylactic dental surgery can now be carried out in patients with hæmophilia. Having taken the precautions outlined, we have no hesitation in removing many teeth in one sitting; and clearance of all remaining teeth has been carried out in 10 patients. Their stay in hospital was not appreciably different from that of others who have had less radical treatment. It must be emphasised, however, that good results can only be obtained through close collaboration between a physician experienced in the management of hæmophilia and the dental surgeon.

Children present two special problems.

The first is that it is sometimes necessary in the hæmophiliac as in normal children to remove sound teeth to correct malocclusion caused by overcrowding. Initially we hesitated to attempt such orthodontic treatment, but with further experience we now consider such operations justifiable. They have been carried out in 8 patients.

Intermittent troublesome dental hæmorrhage when shedding deciduous teeth is the second problem peculiar to the hæmophilic child: it is often the cause of repeated admissions with consequent interruptions of schooling. We found that such multiple admissions could be forestalled by removing all remaining deciduous teeth in children who presented with toothache or hæmorrhage at around their tenth year. We have carried out this treatment in 6 children without complications.

We have no doubt that the technique described has several advantages. Bleeding is usually very slight; postoperative hæmorrhage lasted for an average of 6·6 days in the whole series (range 1–14 days). The length of stay in

hospital is reduced as far as possible (7–15 days). Local anæsthesia in most cases simplifies the operative procedure and provides a better operative field. None of the complications we have seen was serious. Although the use of large amounts of fresh plasma or human A.H.G. must be expected to give better hæmostasis, especially if given immediately before extractions (Nour-Eldin and Wilkinson 1958c), such preparations, apart from being uneconomical, are not essential.

Finkelman (1959) reported that for the extraction of 28 teeth on 11 occasions in one of his hæmophilic patients he had to use a total of 164 blood-transfusions, 8 plasma transfusions, 6950 ml. of autogenous globulin and 17 litres of saline and glucose. It took 3 years and 8 months to complete this work. It is now to be hoped that experiences like this will not be necessary.

Summary

Eighty-one successful dental operations in 58 patients with hæmophilia or Christmas disease have been reviewed. Up to 25 teeth have been removed in one operation.

Good hæmostatic control can be maintained by individually prepared acrylic splints combined with adequate transfusions of fresh blood, without recourse to A.H.G.

The effect of the number and type of teeth extracted, the age of patients, and certain other factors has been studied. Special problems relating to children have been discussed.

Cooperation between physician and dental surgeon is essential for the safety and efficiency of the treatment.

Our thanks are due to Dr. A. C. Bottomley for his help with the statistical analyses; to Dr. F. Stratton and the North Western Blood Transfusion Service; to Dr. H. Lempert and the Clinical Laboratory for making available the large amounts of blood needed; to past and present members of the Department of Hæmatology; and to Dr. R. Ollerenshaw, of the Department of Medical Illustration, for help in preparing the photographs and illustrations.

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JEJUNAL MUCOSA IN IDIOPATHIC STEATORRHŒA

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OBSERVATIONS relating the course of idiopathic steatorrhœa to emotional stress in patients whose personality is akin to that associated with ulcerative colitis (Murray 1930, Groen 1947, Stewart 1949, Paulley 1950) and Crohn's disease (Paulley 1948, 1958) led me to suspect a non-specific jejunitis in steatorrhœa sufferers (Paulley 1949a and b). This ran counter to then held beliefs that the intestinal mucosa is normal in non-tropical sprue (Thaysen 1932) and in tropical sprue (Fairley 1936), but it was in accord with earlier necropsy findings (Thin 1890, Faber 1904, Justi 1913, Manson Bahr 1915, 1924). Later, confirmation was submitted (Paulley 1952a and b, 1954) from jejunal and lymph-node biopsy material taken at 3 laparotomies from patients with idiopathic steatorrhœa.

The mucosa was grossly abnormal, with loss of the villus structure and infiltration with chronic inflammatory cells; the small bowel looked inflamed, and in 1 case œdematous, at operation; and the draining lymph-nodes were enlarged and chronically inflamed. I suggested (Paulley 1954) that, despite Fairley's (1936) negative findings, workers in tropical sprue might find jejunal biopsy similarly rewarding. Unknown to me Milanés et al. (1951) had already done so; and Gardner and Butterworth (1956), Butterworth and Perez-Santiago (1958), and Doniach and Shiner (1957) confirmed the presence of the mucosal abnormality in both the tropical and non-tropical disease. Tubal biopsy (Shiner 1956, Crosby and Kugler 1957, Rubin et al. 1958) has facilitated the mucosal study of the darker reaches of the small bowel, and provided a stimulus to its better understanding.

However, to date there has been no further clarification of the causes of mucosal abnormalities; and from conversations I have had recently in this country and in America it appears that the concept of a chronic non-specific low-grade inflammatory jejunitis is regarded with almost as much scepticism as the psychosomatic observations already referred to (Paulley 1949a, 1952a, 1957, 1959). Anderson and Langford's (1958) negative report on the ætiological significance of intestinal flora in cœliac disease may have increased this.

Past Bacteriological Studies

Bacteriological studies of the small bowel have always been difficult. Intubation carries the risk of contamination of the tube in its passage through the mouth and pharynx; and salivation so induced may also disturb the bacterial flora lower down.

As a result of studies by Cregan and Hayward (1953), Anderson and Langford (1958), and others, it is believed that most of the normal small bowel is nearly sterile; only the upper and lower ends may contain ingressors from the stomach and cæcum. Yet the value of antibiotics in the treatment of the blind-loop syndrome, of the steatorrhœa of Whipple's disease (Paulley 1952b, 1955, Chears 1958) and of Crohn's disease is increasingly accepted. Some patients with idiopathic steatorrhœa have been helped too. Clinicians not unreasonably interpret this as an effect of the antibiotics on the intestinal flora. The antibiotic feeding to animals to promote growth is also a tacit acceptance of the existence of parasitic intestinal bacteria.

Despite these observations we are in complete ignorance as to what organisms in what numbers can be regarded as normal, and what part they may play in disease: nor do we know what protects the intestine against its own organisms following breaches in the epithelial surface. (Lysozyme might be such an agent; but its presence in large amounts in the fæces of patients

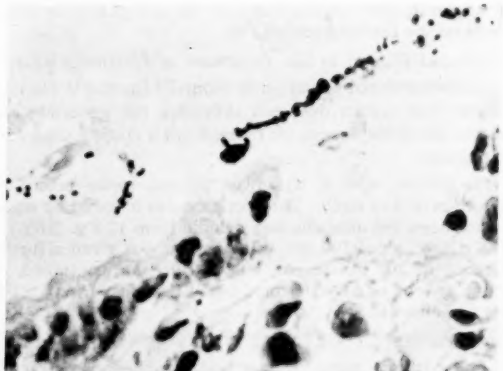

Fig. 1—Idiopathic steatorrhœa. Mucosal border of jejunum: string of gram-positive cocci, superficial erosion, and, at left, diplococci (×800).

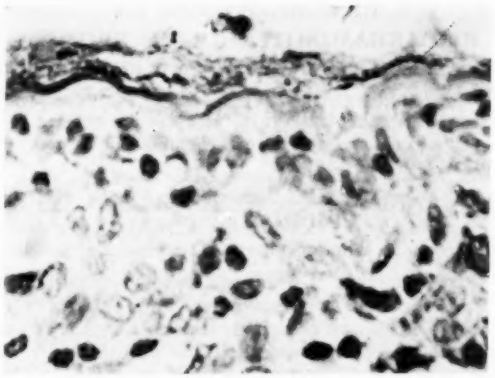

Fig. 2—Idiopathic steatorrhœa. Jejunum: adherent mucofibrinopurulent exudate with organisms in it. Note diplococci and short chain (gram-positive) (×800).

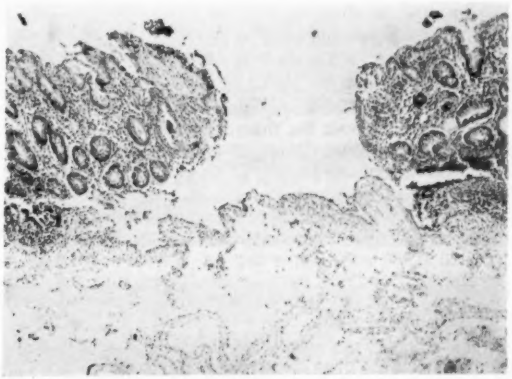

Fig. 3—Idiopathic steatorrhœa. Jejunum: undermined erosion with lymphoid hyperplasia at corners (×50).

with colitis has hitherto suggested an ætiological rather than a protective role.)

Needle aspiration of the small intestine at operation offers an alternative approach (Cregan and Hayward 1953), and this has been performed on the blind loop in a case of blind-loop syndrome (Girdwood and Doig 1957, Card 1959) and I have done so recently in a woman with idiopathic steatorrhœa and folic-acid-deficiency anæmia. *Escherichia coli* was grown from two sites. It is clearly a useful research method, but, now that tube biopsy is available, opportunities for its application in idiopathic steatorrhœa are likely to be few.

Present Investigation

It recently occurred to me that it may be more important to look for bacteria in or on the intestinal wall rather than inside the lumen. Dysentery bacilli are often difficult to grow from fæces but are readily demonstrated after swabbing an ulcer; and sulphonamides which attain a high blood-level and therefore act on the intestinal wall are more effective against them than insoluble ones (Paulley 1942). I therefore decided to examine the mucosa from some severe cases of steatorrhœa using bacterial stains (modified Gram's and Twort's).

Bacteria have been found in 3 out of 7 of the steatorrhœa sections examined, but not in controls taken from normal jejunum at gastrectomy. They were chiefly gram-positive cocci in pairs or short chains. Gram-negative rods have been seen less often.

The bacteria have been found at the free edge of the epithelium, especially in relation to denuded areas with desquamated surface cells (fig. 1).

These areas are numerous in severe cases of idiopathic steatorrhœa. The bacteria and pus cells have been seen both in, and deep to, thin strands of mucofibrinopurulent exudate which was in the process of separation from the mucosal surface (fig. 2). In some instances the strands still reflected the contours of the mucosal surface.

For years I used to believe that this desquamation was caused by section-cutting, and some of it undoubtedly is. Possibly, however, the catarrhal exudate on the slide represents only a fraction of what was there originally, much of it being surely washed away during staining.

An oil-immersion lens and bacterial stains have, therefore, revealed much that was previously hidden. It cannot be decided on the evidence whether bacterial infestation is primary or secondary to damage to the mucosa. On the analogy of colitis, and from observations of psychosomatic factors in colitis and steatorrhœa, I think any bacterial invasion is more likely to be secondary.

Bacteria may be present deep in the crypts, and in the loose columnar epithelium; but, if they are, their identification calls for special technique and experience which I lack.

In 2 sections (figs. 3–5) microscopic erosions or ulcers have also been seen—1 with a purulent exudate but without demonstrable bacteria.

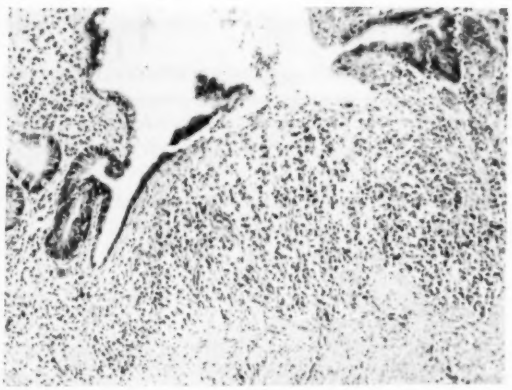

Fig. 4—Idiopathic steatorrhœa. Jejunum: erosion; loss of epithelium; polymorphs and exudate at base (×95).

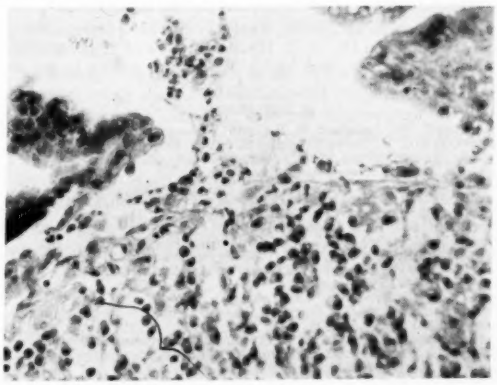

Fig. 5—Idiopathic steatorrhœa. Jejunum: high-power view of fig. 2 showing base of erosion, with loss of epithelium and purulent exudate (×230).

After looking at such sections from time to time for many years I am encouraged to make some histological observations. The main one is that the epithelium in idiopathic steatorrhœa seems to be in a recurrent state of destruction and repair.

This could account for the variable findings in my series and for the inconstant bacterial samples from the intestinal lumen previously reported.

Loss of the normal delicate villus structure, and its replacement by a flattened, sometimes œdematous, mucosa, infiltrated with lymphocytes, plasma cells, and eosinophils, is now widely accepted as the usual biopsy finding. I suggest, however, that atrophy is not the right term for this change, since the depth of mucosa is not necessarily reduced as it is in some patients with post-gastrectomy steatorrhœa.

Microscopy reveals areas of various sizes altogether denuded of epithelium. In these areas epithelial repair takes place from the mouths of decapitated crypts where proliferating columnar cells can be seen pushing upwards and outwards. At some points the new epithelium is barely visible with a low-power lens.

Many of the crypts in steatorrhœa resemble drainpipes when compared with the small normal cavities. They are fewer in a given area and they may be two or three times the usual diameter. The columnar lining cells of the crypts and of the free border lose much of their delicate regularity: they are shorter and without the deep border of translucent cytoplasm. The brush border seems to suffer, too, becoming narrower and shaggier.

The increase in size and reduction in number of the crypts, which are the remains of the normal intervillous spaces, may be of importance; for the crypts are potential sites of absorption in their lower reaches. This phenomenon alone could account for a considerable loss in absorptive area.

Summary

Sections of jejunal mucosa from 7 patients with idiopathic steatorrhœa—3 obtained at laparotomy and 4 by tube biopsy—have been stained for bacteria, which have been shown to be present in 3. A delicate mucofibrinopurulent exudate has been observed at the free epithelial border, especially in relation to denuded areas. In 2 of the sections with no visible bacteria microscopic ulcers were seen; 1 contained leucocytes.

Histologically the mucosa is believed to be in a recurrent state of destruction and repair. Repair apparently takes place by proliferation of columnar epithelium from the mouths of decapitated crypts in the denuded areas.

The study provides further evidence of the existence of a catarrhal type of jejunitis in idiopathic steatorrhœa.

I wish to thank Dr. A. C. Thackray for the photomicrographs, Dr. M. Shiner and Dr. G. D. Hadley for loans of biopsy material to supplement my own, and Mr. S. F. Milner, F.I.M.L.T., for much technical assistance.

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HEXAMETHYLENE 1-6 BISCARBAMINOYLCHOLINE BROMIDE

A NEW SYNTHETIC MUSCLE RELAXANT

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R. P. WISE
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SENIOR REGISTRARS IN THE DEPARTMENT OF ANÆSTHETICS

H. C. CHURCHILL-DAVIDSON
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HEXAMETHYLENE 1-6 biscarbaminoylcholine bromide (' Imbretil ') was synthesised by Klupp et al. (1953) in Austria, and is now commonly used as a muscle relaxant in many European countries. The manufacturers state that the mode of action is " an initial phase, obvious as a depolarisation lasting a few minutes, followed by a persistent paralysis of the curare type " as shown by Herzfeld and Stumpf 1955, Brücke 1956. It is also claimed that the neuromuscular block which it produces can easily be reversed by anticholinesterase substances such as neostigmine or edrophonium.

Despite many pharmacological studies of this drug in animals, and its wide clinical use, evidence of the precise mode of action in man (which is of clinical and theoretical importance, particularly in relation to the use of anticholinesterase drugs) is singularly lacking. We decided, therefore, to study this drug further.

Method

Hexamethylene was given intravenously, in repeated doses of 0·2 mg. per minute, to six conscious volunteers and to ten anæsthetised patients until there was evidence of a 95% paresis of the limb muscles.

In the conscious state all subjective symptoms, such as fasciculations, were noted, the grip-strength was measured with an ergometer, and the vital capacity and tidal volume were recorded with a gas-meter and spirometer.

In the anæsthetised patients (premedicated with papaveretum 10 mg. and hyoscine 0·45 mg.) the induction was undertaken with thiopentone (0·5–0·75 g.) followed by nitrous oxide/oxygen (6/2 litres) in a semiclosed circuit, with the addition of pethidine hydrochloride (25–75 mg.). All other relaxant and inhalational agents were avoided.

Electromyographic (E.M.G.) measurements were made in every case. Applying the technique already described (Churchill-Davidson and Christie 1959), the following were studied:

1. The degree and duration of neuromuscular block in relation to the dose.

2. The ability to maintain successive stimuli at various rates.

3. The presence or absence of post-tetanic facilitation (i.e., the height of a single action potential recorded after a burst of tetanic stimulation compared with that before stimulation).

DR. PAULLEY: REFERENCES (*continued*)

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4. The effect of anticholinesterase therapy on the neuromuscular block.

An intravenous injection of edrophonium 10 mg. was used as an anticholinesterase drug in conscious subjects, and neostigmine 2·5 mg. (preceded by atropine sulphate 1 mg.) in the anæsthetised patients.

Results

An intravenous injection of 1·0–1·5 mg. (0·005 mg. per lb. body-weight) of hexamethylene produced a 95% reduction in neuromuscular transmission both on volitional (fig. 1) and on E.M.G. measurement. The duration of the paresis to approximately 75% recovery was 28 minutes.

After injection five of the six conscious subjects complained of fasciculations in the neck, back, and legs. Vital capacity measurements were reduced by 12–25% at the height of the paralysis, but there was no change in the tidal volume. The blood-pressure and pulse-rate were unaltered.

E.M.G. studies revealed the following:

1. The action potential was well maintained, even with fast rates of nerve stimulation (compare figs. 2a and b).
2. There was no evidence of post-tetanic facilitation (fig. 2b).
3. The intravenous administration of edrophonium or neostigmine led to a potentiation of the block (fig. 2c).

Discussion

The results of injecting a single paralysing dose of hexamethylene show three main features. Firstly, there

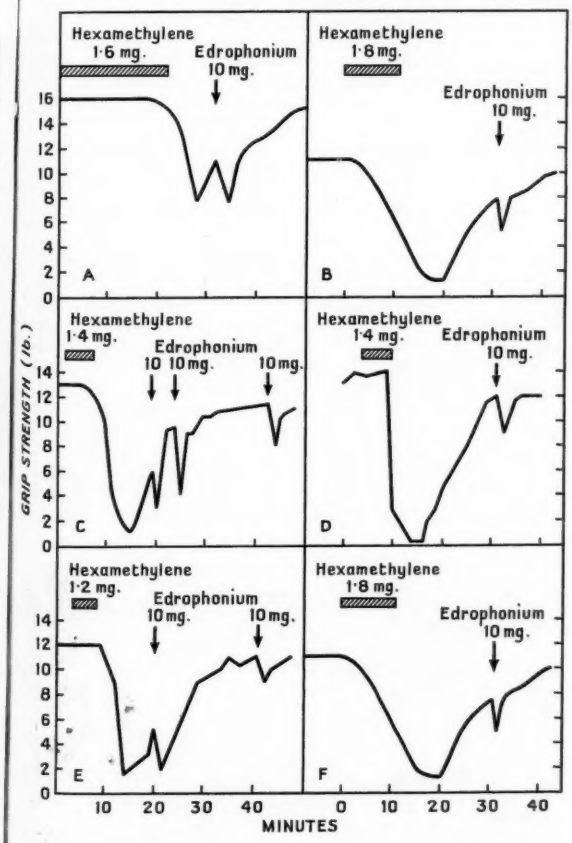

Fig. 1—Effect on grip strength in six conscious volunteers of hexamethylene followed by edrophonium.

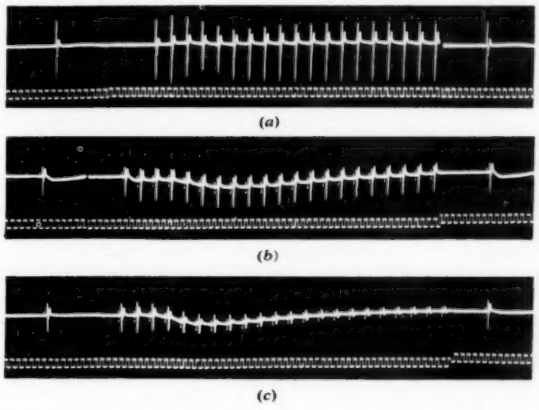

Fig. 2—(a) Control tracing; (b) 10 minutes after hexamethylene 1·5 mg.; (c) continuation of (b) 4 minutes after injection of neostigmine 2·5 mg.

were fasciculations in muscles throughout the body. Secondly, E.M.G. measurements revealed a depolarising type of neuromuscular block which persisted until complete recovery. Thirdly, injection of an anticholinesterase drug during the period of paresis was always followed by signs of further neuromuscular blockade.

Despite the pharmacological findings in animals (Brücke 1956, Klupp et al. 1953), and the previous clinical trials (Brücke and Reis 1954, Reis 1955), these results prove that the action of hexamethylene in man is similar to that of decamethonium and suxamethonium. It must, therefore, be regarded as a depolarising muscle relaxant, although there is evidence that repeated doses of a depolarising drug such as suxamethonium may lead to an alteration in the type of neuromuscular block in man (Churchill-Davidson and Christie 1959). But it would be premature to say that this change is necessarily one of true non-depolarisation.

Clinically it is most important to know the type of neuromuscular block present at any particular time, as the injection of neostigmine will increase a depolarising block, yet reverse one due to non-depolarisation (such as that produced by tubocurarine). The clinical impression that neostigmine reverses the neuromuscular block produced by hexamethylene must be explained. There are three possible causes:

(1) The action of hexamethylene on the muscles of respiration may differ from that on the limb muscles. This seems highly unlikely.

(2) Neostigmine may stimulate respiration through some mechanism other than the inhibition of cholinesterase at the neuromuscular junction. The activity of neostigmine is widespread, and, even when preceded by large doses of atropine (1–2 mg.) it produces the most unpleasant sequelæ (e.g., severe colic and vomiting) in conscious subjects. The side-effects of this drug may, therefore, stimulate respiration peripherally.

(3) Repeated doses of hexamethylene, such as are often required in practice, may lead to a gradual change in the type of neuromuscular block from one of depolarisation to one of non-depolarisation (dual block). This response clearly follows the use of other depolarising drugs such as decamethonium or suxamethonium, but it depends on several factors, including the total dosage used and the time-interval between successive doses. The use of an anticholinesterase in an attempt to reverse a supposed " dual block " is justified only if there is absolute proof that the neuromuscular transmission has undergone this change.

This new synthetic relaxant drug illustrates the extreme care needed in analysing the action of such drugs in man before their widespread clinical application.

Summary

The intravenous injection in man of a single paralysing dose of a new synthetic muscle relaxant—hexamethylene 1-6 biscarbaminoylcholine bromide—produced a depolarising type of neuromuscular block. Furthermore, an injection of an anticholinesterase drug at any time during the recovery phase led to a potentiation of the neuromuscular block.

We are grateful to the endowment funds committee of St. Thomas's Hospital for a grant to buy apparatus for this work. Supplies of hexamethylene 1-6 biscarbaminoylcholine bromide (' Imbretil ') were kindly provided by Stickstoffwerke, Linz, Austria.

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New Inventions

A PORTABLE ANÆSTHETIC MACHINE

A LIGHTWEIGHT, simple, yet versatile and economically priced Boyle's apparatus would be useful in hospital, private, and domiciliary practice. That described and illustrated here weighs only 7 lb., holds up to 72 gallons of oxygen and 400 gallons of nitrous oxide, and can be easily carried in the hand. Made of standard components, it can—if the need arises—be connected to any available size of pin-index cylinder. Its basis is a combined regulator/flow-meter unit. This consists of a cylinder yoke with a non-return valve, a light-alloy pressure-reducing valve, a control tap, and a plastic flow-meter with a rotating bobbin which is easily seen from any direction. (These units are available for most gases and a number of flow ranges.)

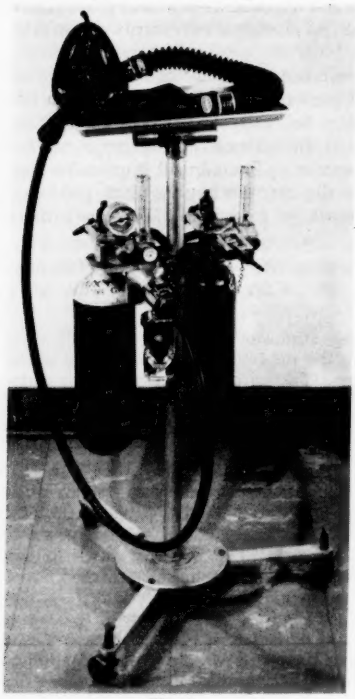

Fig. 1.

The stand consists of a central castor, which supports the weight, with feet for stabilisation. It can be folded to carry in a bag or car, but it cannot collapse accidentally. A tray can be fitted to the carrying handle when the apparatus is in use (fig. 1).

A regulator unit with a cylinder-contents gauge is used for oxygen; for nitrous oxide the regulator has a double yoke, allowing instant change from one cylinder to the reserve (fig. 2). A socket on the stand will take any standard vaporising bottle, but the Rowbotham bottle, which is small and not easily damaged, is recommended. If the Waters canister assembly has a

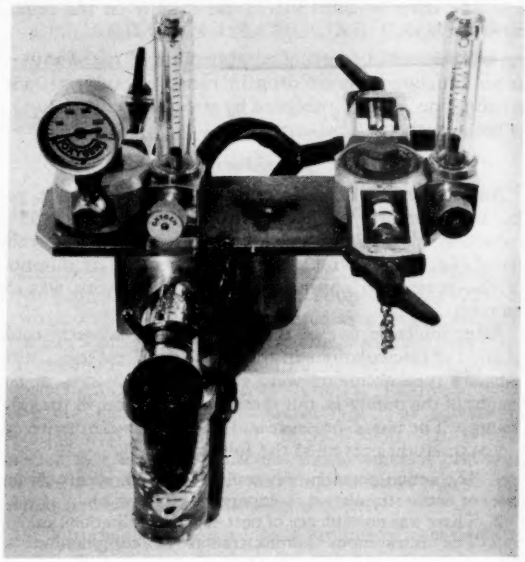

Fig. 2.

double-ended bag an alternative semi-open system can be made, using the corrugated extension tube and feeding the gases into the bottom of the bag, as shown in fig. 1. The gas cylinders are not connected via tubing to the flow-meter unit, so that the risk of fitting the wrong cylinder is minimised.

The cylinders must be held vertically for the flow-meters to operate. The stand described does this conveniently, but any method may be used depending upon the particular requirements.

The flow-meter units are made by Airmed.

Department of Anæsthetics,
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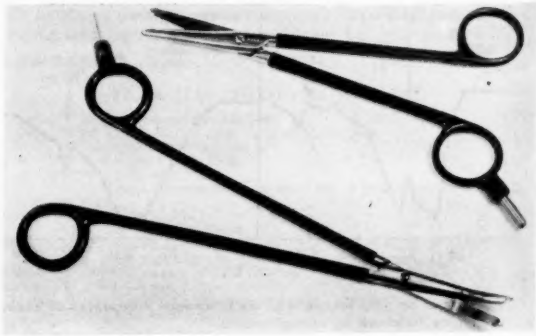
J. D. K. BURTON
M.B. Lond., F.F.A. R.C.S., D.A.

COMBINED DIATHERMY FORCEPS AND SCISSORS

A SURGICAL scissors has been designed with blades which are tipped with a diminutive forceps grip, thus allowing scissors dissection and diathermy coagulation to be done with the same instrument. The instrument is designed for diathermy in the usual way by insulation of the handles and by provision of an attachment on one of the finger rings for the cable. Two patterns of this diathermy scissors are shown in the figure. One is an 8 in. straight scissors suitable for surface work; the other is a 10 in. slender scissors with small curved blades designed for deep dissection.

Hæmostasis is achieved by cutting a segment of vascular tissue and then coagulating the bleeding-points or by coagulating an isolated segment of vascular tissue before cutting it.



Cutting and coagulating simultaneously is not wholly effective for hæmostasis. Although the blades do not cut right up to the tips the use of the scissors can be accommodated to this limitation. The straight scissors expedite hæmostasis in muscle section and operations such as the perineal part of an excision of rectum. The long scissors maintain a dry field in deep and difficult dissections and save time. Gentle insinuation of the tips of the blades under moieties of tissue by the familiar movement of slowly opening and closing the blades isolates strand after strand of potentially vascular tissue for division and immediate hæmostasis. In this way the diathermy forceps and scissors simplifies operations on the biliary tract, abdominothoracic operations, the abdominal part of an abdominoperineal excision of the rectum, adrenalectomy, &c. Indeed the adrenal gland can be dissected and excised solely with this instrument.

These instruments have been made for me by Murphy Boyle, Ltd., 69, Wimpole Street, London, W.1.

Whipps Cross Hospital, London, E.11 D. LANG STEVENSON. F.R.C.S.E.

A DEVICE FOR FLAMING PLATINUM LOOPS

VARIOUS anti-sputter devices for the safe flaming of platinum loops are obtainable commercially. These consist of a cylindrical shield surrounding the Bunsen flame, with an orifice at the side or at one end, for the insertion of the loop. Generally speaking they have the disadvantage of being bulky and hot, and some of them prevent the flame from being used simultaneously for any other purpose. In addition, there is the possibility of the escape of resistant viable bacteria on the updraught of hot air.

The appliance illustrated here consists of a stainless-steel tube $4^1/_2$ in. long, with an internal diameter of $^7/_{16}$ in. and a wall thickness of not more than $^1/_{32}$ in. The lower end of the tube is closed, and the upper end expanded to form a funnel, which is partially occluded by an annular baffle, thus forming a spark-guard after the fashion of the early wood-burning locomotives. The tube is held at an angle of 45° in the hottest part of the Bunsen flame by an adjustable clamp attached to the barrel of the burner.

Stainless steel was chosen after trials with several other materials because of its resistance to corrosion and absence of the formation of bacteriostatic oxides, which might contaminate the loop. Transparent materials, such as silica, proved unsuitable because they failed to become hot enough, were too fragile, and developed an opaque patina, which defeated the advantage of transparency.

The apparatus was tested with large loops, inoculated with heavy broth suspensions of bacteria, aqueous suspensions of spores, and semi-solid aggregates scraped from agar cultures. The test organisms included *Mycobacterium phleii* and spores of *Bacillus anthracis*. Open agar plates were placed immediately below the mouth of the tube to catch gravitating particles, and the air vertically above was sampled through an extension fitted to a slit-sampler orifice. No vegetative organisms escaped, but occasional spores produced colonies both on the gravity plates and in air samples. This happened when a contaminated part of the wire or holder remained outside the tube; it can arise with other types of apparatus, and can be avoided. The trials were intentionally far more rigorous than is likely in practice. The procedure was no less convenient than sterilisation in the open flame, but a small carbonised residue sometimes required burning off.

I am grateful to Mr. G. H. Clement for constructing this appliance.

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Microbiological Research Establishment, Ministry of Supply, Porton, near Salisbury, Wilts. H. M. DARLOW B.A. Cantab., M.R.C.S.

Reviews of Books

Bronchography

C. DIJKSTRA, M.D., medical superintendent, " De Klokkenberg " Sanatorium and Chest Hospital, Breda, The Netherlands. Oxford: Blackwell Scientific Publications. 1959. Pp. 157. 45*s*.

BRONCHOGRAPHY is an investigation widely used today in very many conditions and yet there seems to be little agreement about the best method of performing it. Dr. Dijkstra favours intubation of the trachea through a nostril using a catheter opaque to X rays and under fluoroscopic control. This is a method which has many adherents, but it would be interesting to know the proportion of cases in which it fails and also what alternative Dr. Dijkstra keeps up his sleeve. He describes a specially designed and very simply made tilting table on which the patient lies with the side to be examined downwards, and with the dependant arm comfortably dangling through a hole in the table top. This table is narrow enough to be used behind a fluorescent screen if necessary and it does away with much manhandling of heavy patients when the various lobes of the lung are being filled. There is certainly a place for an aid of this sort in most departments where bronchography is done. Dr. Dijkstra is perhaps a little unorthodox in using as contrast medium a mixture of lipiodol and powdered sulphonamide rather than the now more commonly used propyliodone ('Dionosil '). The mixture is said to minimise the two main drawbacks to lipiodol alone—alveolar filling (and retention) and iodine reactions. Dr. Dijkstra rightly recalls that there are real hazards to the life of the patient in bronchography both from the contrast medium and from the local anæsthetic, whatever choice is made, and mentions some of the precautions (but by no means all) which it is prudent for the operator to take.

The book is attractive to handle, and the illustrations of the various bronchographic appearances are admirably clear. It is all laid out rather like an atlas and the common conditions in which bronchography is likely to be helpful are presented as well-documented cases. Dr. Dijkstra is not writing for special departments: it is his aim to introduce bronchography to the increasing number of doctors who are now called upon to practise the technique. His book succeeds fully and should be particularly helpful to radiologists and chest physicians.

The Mast Cells

JAMES F. RILEY, M.D., PH.D., D.M.R.T., consultant radiotherapist, Royal Infirmary, Dundee, lecturer in radiotherapy, University of St. Andrews. Edinburgh: E. & S. Livingstone. 1959. Pp. 182. 30*s*.

MAST cells are interesting constituents of connective tissue and blood (where they are better known as basophil leucocytes). They are far more abundant in tissues than in blood, and they, or comparable cells, are found in many genera, both invertebrate and vertebrate. In the human embryo they occur in high concentration in liver, heart-muscle, and vessels, in developing thymus, and in all subcutaneous connective tissue. In the adult they are common in submucous and loose cutaneous connective tissue and are found concentrated around blood-vessels. The central nervous system lacks mast cells, but they are to be seen in the sheaths of the peripheral nerves. The cells contain at least two substances of great interest—histamine and heparin. The cells were first given differential recognition by Ehrlich in 1879, and following this a considerable volume of histological work appeared. But it is only in recent years that the function of these cells has been intensively studied, and much of the work is the outcome of the interest and activity of Dr. Riley and his coworkers.

The appearance of this monograph by Dr. Riley himself is very welcome. He gives a clear account of the history of the subject and a review of much of the literature, and then proceeds to describe and discuss the experimental work on which he has built a hypothesis of mast-cell function. He

examined, either by himself or with colleagues, the distribution of mast cells in the tissues of several vertebrate species, and showed clearly the close positive correlation which exists between the histamine content of a tissue and the number of mast cells it contains. He also found a strongly positive correlation between histamine and mast-cell content of certain pathological tissues, as in urticaria pigmentosa in man and some mast-cell tumours in domestic animals. He tackled the problem of the site of storage in, and liberation of histamine from, mast cells. From a study of the specific and non-specific substances which release histamine, and by direct observation of their action on the cells, he concludes that histamine exists in mast cells preformed in the granules and ready for release. He points out that histamine can also be held bound in tissues in which there are but few mast cells, as in the pyloric mucosa.

The story of the relationship between mast cells and heparin is as yet less clear. In the dog, peptone shock is accompanied by a reduction in blood coagulability following the release of heparin as well as histamine from the mast cells. In the other animals studied shock is not accompanied by decreased coagulability; further, histamine liberators release only about half the heparin present in mast cells. The question arises whether heparin from tissue mast cells is a natural anti-coagulant, or has an altogether different function, as Dr. Riley believes, and that the presence of heparin in the cells is related to the fresh formation of ground substance by connective-tissue cells. He suggests that, to this end, mast cells store and release mucopolysaccharides, and that heparin is the storage form. One omission from the book is discussion of the lipæmia-clearing reaction of heparin, and whether this heparin could come from blood-borne or perivascular mast cells, and, further, whether the heparin of mast cells in adipose tissue is concerned with the laying-down of fat or its removal for metabolic purposes. Considering Dr. Riley's experience, it would have been useful to have his views on this aspect of the heparin problem.

This monograph is interesting, well written, beautifully produced, and inexpensive. It can be strongly recommended.

The Organic Psychoses

JOHN G. DEWAN, M.D., PH.D. D.P.M. F.R.C.P.C., F.A.C.P., F.A.P.A., associate professor of psychiatry, University of Toronto, director, outpatient department, Toronto Psychiatric Hospital; WILLIAM B. SPAULDING, M.D., F.R.C.P.C., associate professor of medicine, and associate, department of psychiatry, University of Toronto, physician in charge of medical outpatient department, Toronto General Hospital. Toronto: University of Toronto Press. London: Oxford University Press. 1958. Pp. 170. 48*s*.

EMERGENCY medicine and emergency psychiatry involve care of such differing sorts that, as Professor Aldwyn Stokes says in the preface, optimum facilities for the care of very disturbed patients, and for their diagnosis and physical investigation, do not so often coincide. The authors give brief medical accounts of a large number of disorders causing mental symptoms although they are somewhat courageously over-simple in their psychiatric descriptions. It is perhaps better, however, in such a short work, to emphasise the cardinal points and not distract with detail—fuller clinical accounts of the organic states are to be found in such standard works as, for example, that of Professor Mayer-Gross and his colleagues.[1] The book is at its best in the discussion of 27 illustrative case-histories showing some of the pitfalls which beset the psychiatrist faced with an early organic case. A large number of references are given to the conditions mentioned and there is a list of technical procedures. This work will be useful to doctors entering medicine and psychiatry, especially those starting work in observation wards, and it should be particularly recommended to those psychiatrists who feel a thorough grounding in organic medicine to be of little relevance to their art.

1. Mayer-Gross, W., Slater, E., Roth, M. Textbook of Psychiatry. London, 1955.

Surgery of the Prostate

HENRY M. WEYRAUCH, M.D., F.A.C.S., clinical professor of surgery (urology); chief, division of urology, Stanford University School of Medicine. Philadelphia and London: W. B. Saunders. 1959. Pp. 535. 105*s*.

THE rapid advances in prostatic surgery make the appearance of this volume particularly opportune. The standards of urological treatment for prostatic obstruction vary considerably, being largely influenced by the availability of urological centres and facilities for postgraduate training. While early and selective specialisation may sometimes favour blind acceptance of a particular technique, inadequate experience and a rigid adherence to outmoded methods are often an even greater bar to progress.

Professor Weyrauch has sought to present an up-to-date account of the full range of prostatic surgery; and this volume will interest all urologists and particularly their assistants and those embarking on a career in this specialty. Preliminary sections on the pathology and symptomatology of prostatic disease are succeeded by descriptions of the techniques of prostatectomy which are well illustrated and, on the whole, satisfyingly free from personal bias.

Healthier Babies—Happier Parents

HENRY K. SILVER, M.D., C. HENRY KEMPE, M.D., RUTH S. KEMPE, M.D., department of paediatrics, University of Colorado; with a foreword by PHILIP EVANS, M.D., F.R.C.P. London: Collins. 1959. Pp. 225. 8*s*. 6*d*.

HERE, in the format of a child's picture-book, is a sane and well-informed book of infant and child welfare, compiled in the U.S.A. but so "Englished" as to leave little internal evidence of its country of origin. The book is in two parts, a "handbook", written cursively, taking parents and child from its birth to its fourth year, and a second part, in question and answer, covering the first twelve months in detail. Normal upbringing, progress, and hygiene and the common problems and misadventures of infancy are considered with good sense and restraint and with commendable respect for the province of the family doctor. Instruction in the technique of breast-feeding is good, though its practice is very tepidly commended. The book is "decorated with more than 100 light-hearted drawings". They seem to represent a violent swing from pretti- to slutti-fication of their subject. Babies have acne; mothers no chins; both are constantly in a mess. Why not leave them out?

Viral and Rickettsial Infections of Man (3rd ed. London: Pitman Medical Publishing Co. 1959. Pp. 967. 63*s*.).—The third edition of this well-known reference work, edited by Dr. T. M. Rivers and Dr. F. L. Horsfall, appears seven years after the second, at a time when rapid strides in virology have made it necessary to rewrite the text entirely. There are some new chapters and new contributors, and the tone of the book has changed considerably. Again, nearly the first third of the book is devoted to general aspects of virus growth and laboratory methods, but there is now much emphasis on tissue-culture techniques in virology and on biochemical aspects of virus growth. Particularly good chapters are those by S. S. Cohen, A. D. Hershey, and J. F. Enders. One fault in the second edition was the illogical arrangement and this has now been partly remedied. The chapter on poliomyelitis has been expanded into three chapters which deal with general aspects, pathogenesis, and control of this disease (H. A. Howe and J. L. Wilson, D. Bodian, and J. E. Salk). Many new viruses have been isolated since the second edition, including the ECHO group, adenovirus, measles virus, and a number of arthropod-borne viruses, and these are all dealt with thoroughly; but even since this edition went to press trachoma and several new respiratory viruses have been cultured. This third edition is a most successful attempt to keep pace with a rapidly growing subject, and it is certain to satisfy a need among bacteriologists and virologists.

THE LANCET

LONDON 24 OCTOBER 1959

Diabetic Retinopathy

IN the past half-century the whole pattern of disease produced by diabetes mellitus has changed. Not only has the expectation of life of diabetics been greatly increased but the causes of their ill health and deaths have been altered. Whereas before the 1914–18 war the commonest cause of death was diabetic coma, it is now atheromatous disease and renal failure. Previously much of the diabetic's ill health was due to chronic infection—tuberculosis and osteomyelitis—but now it is due to neuropathy and retinopathy. Of these, retinopathy seems particularly important to study; for it develops in all kinds of diabetics, young and old, mild and severe, fat and thin, and may destroy vision and with it much of the pleasure of life many years before the patient's death. Once it has developed there is no curative treatment; and although in general the better the control the less likely is retinopathy to develop, complete control does not necessarily provide complete protection. It has been suggested that the changes in the eyes in diabetics simply reflect another aspect of diabetic disease—that these changes are caused by what causes diabetes, not by the diabetes itself. But the occurrence of typical retinopathy in diabetes known to be secondary to chronic pancreatitis gives the lie to this and raises the question: What is the disturbance imposed by diabetes mellitus which causes these highly specific and localised changes?

The sequence of events leading to diabetic retinopathy is well established. The earliest changes are probably in the veins in the macula, which become varicose.[1] Next, small red dots appear in the posterior polar region; these have been shown to be due to the formation of capillary microaneurysms [2] which spread and eventually may affect the whole retina. Exudates containing lipid form close to some of the aneurysms, and are seen as yellowish-white patches. New vessels may form, appearing as a delicate intravitreal network overlying areas of retinal ischæmia. Hæmorrhage may occur, either behind the hyaloid membrane or bursting through into the vitreous, and may become organised and vascularised (retinitis proliferans). The characteristic lesion is clearly the microaneurysm. Similar aneurysms have been sought elsewhere in the body, but have been found only in the conjunctiva; and this observation has been shown to be unrelated to diabetes mellitus.[3] Retinal microaneurysms arise in some other diseases—for instance, malignant hypertension (where they are unusual) and Eales' disease (a condition marked by repeated hæmorrhages into the retina and vitreous). Typical microaneurysms are found also in thrombosis of the central retinal vein and in sickle-cell/hæmoglobin-C disease; in both cases there are strong reasons for regarding the fundamental lesion as retinal venous obstruction. Attempts to relate microaneurysms to disordered fat or mucoprotein metabolism (both well recognised in diabetes) fail to explain either the specificity of the changes or their localisation to the retina.

Thus the only apparent clues to the formation of microaneurysms and their localisation to the retina is local venous obstruction. With this clue, and a detailed knowledge derived from experimental pathology, ASHTON (to whose work so much of this knowledge is due) reasoned that in diabetes mellitus there might be some retinal capillary obstruction caused by swelling of the surrounding retinal cells. This would presumably be due to the imbibition of water by the cells consequent on interruption of their normal metabolism, these cells being known to depend largely on glucose for energy.

In support of this theory Professor ASHTON has mobilised considerable indirect evidence. In an article published in this issue (p. 625) he sets out six points derived from experimental studies in kittens and rats which indicate strongly that cells deep in the retina may, when their metabolism is deranged, swell and thus produce retinal vascular changes. He draws attention to an old observation [4] that the first effect of acute central retinal arterial obstruction is to produce a milky white opacity, most noticeable at the posterior pole. This is reversible if the circulation is restored in time, and is thought to be due to transient œdema. ASHTON himself has shown that the cotton-wool patches in malignant hypertension are grossly swollen nerve-fibres in areas of retinal ischæmia. Moreover, it is close to these areas that microaneurysms may develop.

Accordingly the causal lesion in diabetic retinopathy may be swelling of cells deep in the retina—swelling caused by deranged metabolism. There are, as ASHTON says, objections to such a theory; but it would help to explain why retinopathy is common in badly controlled diabetics, and it directs the attention of research-workers to the site of the initial lesion in diabetes mellitus—the cells themselves.

Operations for Chronic Myocardial Ischæmia

IN the surgical relief of myocardial ischæmia, one of the big opportunities for cardiac surgery, progress has been slow despite many years of continuous experiment. The pioneer work of BECK [5 6] in the United States and O'SHAUGHNESSY [7 8] in this country in the 1930s held out great promise, but today results are very little better than those achieved over twenty years ago. The aim of some operations was to graft omentum or muscle on the myocardium in order to bring to it an extra blood-

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7. O'Shaughnessy, L. *Brit. J. Surg.* 1936, **23**, 665.
8. O'Shaughnessy, L. *Lancet*, 1937, **i**, 185.

supply. Other methods abraded the epicardium, and irritant substances, such as talc, were added in order to obliterate the pericardial space, in the hope that blood-vessels would grow into the adhesions. Although there was evidence of symptomatic improvement, there have been disappointingly few signs that such blood-vessels were in fact produced. In their paper this week Dr. KAUNTZE, Dr. MCGILL, and Sir RUSSELL BROCK, using these techniques, illustrate this point. It is clear from the work of many investigators that a satisfactory method of introducing a new blood-supply to the heart has not yet been achieved, but this is not to say that many patients have not benefited considerably from one or other of the operations.

Although there is little evidence that anastomoses can develop across the pericardium to the myocardium, YATER et al.[9] suggested that irritative measures applied to the epicardium stimulated intercoronary anastomosis. A similar result follows constriction of the coronary sinus. It is not at all clear why this should be, but several workers have produced injected specimens showing an apparent increase in these anastomoses. After many years of experiment with internal-mammary implants into the myocardium, and more recently with ivalon-sponge prosthesis attached to the myocardium, VINEBERG et al. [10 11] have demonstrated anastomoses of vessels outside the heart to those in the myocardium itself, and the development of the myocardial sponge (i.e., increasing the blood sinusoids between the muscle bundles); but no-one has yet definitely shown which way the blood flows in these vessels. Anatomical demonstration by postmortem injection is not enough, and further work must be done on the direction of flow. VON WEDEL'S [12] findings do not suggest that blood is transferred from the internal mammary system to the heart by means of skin-graft attached to the heart. On the other hand, BAILEY et al.[13] refer to CHARDACK'S more hopeful data.

In the normal heart the head of pressure in the coronary vessels is probably greater than that in any peripheral vessels that may be grafted to the heart; but the balance may be altered by blocking in the coronary vessels, so that blood can reach the heart via the grafted vessels. The difficulty here is the old one of trying to reproduce a human disease in the laboratory animal, in order to make accurate measurements. As BECK et al. state, even 4–6 ml. of blood per minute is valuable to an ischæmic heart, but would have no effect on the normal heart. This small quantity of blood may considerably reduce immediate mortality after an occlusion, because it cuts down the size of the anoxic area, which may act as the trigger for ventricular fibrillation. Thus, grafting tissue on the heart has been disappointing; and the actual insertion of vessels into the heart is still under investigation, and nothing conclusive has yet emerged. There is a third approach—direct attack on the coronary vessels themselves—which has been attempted in recent years in the United States, [14–16] and was referred to at a recent meeting of the American College of Surgeons (p. 664). The claim is that by operating directly on the heart, usually with a heart-lung machine, the block in the coronary artery can be located and removed. This seems to be the most logical approach, but the reported proportion of hearts with isolated lesions amenable to surgery varies from 13 to 90%. With improved radiographic techniques, it should be possible to secure much better coronary arteriograms, which are essential before surgical attack on a blocked vessel. Unfortunately, the risk of coronary arteriography in patients with obstructed coronary arteries is still rather high. The actual operation of removing the block by techniques such as re-boring is not too difficult, and the grafting of an autograft or a homograft artery to replace the block is not impossible.[17 18] A fourth device is to ligate the internal mammary artery below the pericardiacophrenic branch [19 20] to increase blood-supply to the heart, and this step is included in the operation used by Dr. KAUNTZE and his colleagues. It does not, however, seem to have stood the test of time, though many good results have been claimed for this simple ligation; but equal improvement has been noted in patients who have had a " blind " operation, such as a skin incision in the area of internal mammary ligation, when the patient was unaware that he had not had the full operation.

On balance there seems to be a place for *some* operation in carefully selected patients with severe angina. Operation often leaves them with an increased exercise tolerance, and encouraging results can sometimes be obtained by a relatively minor operation. The suggestion of BAILEY and others that these operations interfere with transmission of pain impulses from the surface of the heart is reasonable, for many patients are dramatically improved immediately after operation, long before blood-vessels of any size can develop. Moreover, sympathectomy gives similar results and was one of the first operations used for anginal pain. It is perhaps significant that all the experimental methods used in the dog, where the standard test is ligation of the anterior descending branch of the left coronary artery (producing a mortality of about 80% in the unprotected animal), gave a similar survival-rate of about 70% in treated animals [21]; and no one operation showed a significant advantage over any other. Even if surgery provides effective relief in the near future, the final treatment of this disease will almost certainly turn out to be biochemical.

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Medical Costs in Perspective

IN 1953, in view of widespread concern about the rising cost of medical care, the International Labour Office [1] undertook a study of social security schemes in different countries. In its report [2] I.L.O. presents a well-ordered mass of data, and after taking account of possible pitfalls, draws a number of conclusions which neither opponents nor supporters of the National Health Service should ignore. Their first observation is that all the developed countries tend to spend about the same percentage of their national income on medical care, no matter how this is financed:

> 4·06% for Belgium (1954); 4·41% for Canada (1953); 3·67% for Denmark (1952–53); 4·43% for France (1952); 3·76% for the Netherlands (1953); 4·56% for New Zealand (1953); 4·48% for Norway (1955); 4·48% for the United States (1953); and 4·05% for England and Wales (1953–54).

Though these figures give no indication of the quality of medical care in Britain compared with that in other countries, they at least suggest that the N.H.S. is not relatively expensive.

The share of the cost of medical care borne by social-security schemes ranged from as little as 25% to as much as 95%. This variation depended partly on the range of services offered and contributions received, but chiefly on how much responsibility the public authorities assumed for financing hospital care. The main variations in the *total* cost were due to differences in the costs of pharmaceutical supplies and specialist care; and the amount spent on specialist care seemed to be directly related to the amount spent on pharmaceutical supplies.

In themselves social-security schemes do not seem to increase national expenditure on medical care: they only replace expenditure from other sources, and the total cost is no higher than when medical care is provided by private practice supplemented by public finds in cases of need. Indeed the report shows that whatever increase there has been in medical costs is largely illusory. Hospital costs tend to rise more sharply than the cost of other forms of medical care, but national totals have not in fact risen faster than national incomes or wages. The I.L.O. findings thus support the suggestion which Dr. SEALE [3] lately put forward in our columns that the proportion of the gross national product which a nation devotes to medical care tends to remain constant.

The report shows that the share of our national income which has gone to the N.H.S. contrasts unhappily with the share allotted to similar schemes in other countries, where during the late 'forties and 'fifties it has at least remained stable—only in England and Wales has there been a clear fall. This suggests that it might be wise to consider carefully Dr. SEALE's warning that in a nation where nearly all medical care is under central financial control the natural self-adjusting balance may be disturbed. Should we not also go on to consider whether the £400 million ceiling which was arbitrarily fixed for the N.H.S. in 1950 has not already had something of this effect? The Ministry of Health [4] itself has pointed out that during 1948–58 pay and price changes probably accounted for nearly three-quarters of what rise there has been in the cost of the N.H.S. The Guillebaud Committee [5] has not been alone in expressing misgivings that the N.H.S. is being skimped for cash while most of Britain prospers. Efforts to keep expenditure as close as possible to the 1950 ceiling of £400 million may have been fairly effective, but with a rising national income they may have also been misplaced. In a country such as ours, expenditure expressed as a proportion of national income seems to be a more realistic guide to cost of medical care than an arbitrary and rigid limit, and the I.L.O. report offers impartial guidance which could be helpful in replacing the N.H.S.'s outmoded ceiling by a more up-to-date financial cover.

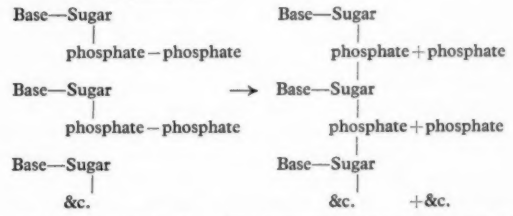
1. The International Labour Office is part of the International Labour Organisation, which is one of the specialised agencies of the United Nations. 80 countries are members; and representatives of governments, of management, and of labour organisations share in its work.
2. International Labour Office. Cost of Medical Care. Geneva. 1959. Pp. 216. 9s. (Obtainable from the London office of I.L.O., 38–39, Parliament Street, S.W.1.)
3. Seale, J. R. *Lancet*, Oct. 10, 1959, p. 555.

Annotations

NOBEL PRIZEWINNERS

THE widespread scientific interest in the cellular nucleic acids is again indicated by the award of the 1959 Nobel prize in medicine to the American biochemists, Dr. A. Kornberg and Dr. S. Ochoa.[6] Thus only two years after the award to Sir Alexander Todd for his work on the chemical synthesis of the fundamental building units of the nucleic acids, the biochemical synthesis of the macromolecules from these building blocks has been similarly recognised.

In 1956 Ochoa and his colleagues reported that a soluble extract of some bacteria was able to carry out the following synthesis:

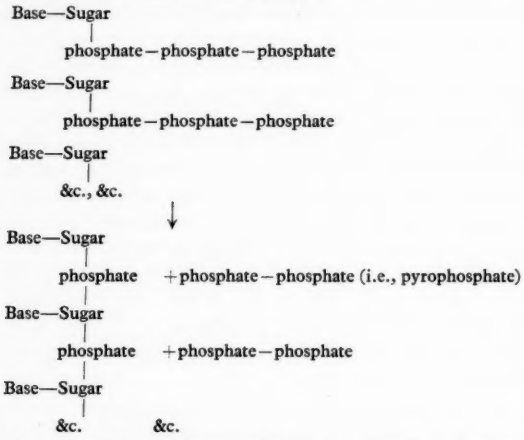


This was originally demonstrated with a single substrate (adenosine diphosphate where the indicated base is adenine); but it was later shown that a mixture of the ribose diphosphates of the four organic bases—adenine, guanine, cytosine, and uracil—which occur naturally in all specimens of ribonucleic acid could be copolymerised to form a polymeric material indistinguishable from the ribonucleic acids present in the cytoplasm and nucleolus of cells. The polymer even adopted the typical two-stranded helix of the natural molecules.[7]

Ochoa's work on ribonucleic acid synthesis has been paralleled by Kornberg's work on the corresponding nuclear material, desoxyribonucleic acid, long identified as the carrier of genic information. In this investigation, the building units were the triphosphates of the base-

4. *Rep. Min. Hlth, Lond.* 1958, para 1, p. 220.
5. Report of the Committee of Enquiry into the Cost of the National Health Service; para 21. H.M. Stationery Office, 1956.
6. See Kornberg, A. *Advanc. Enzym.* 1957, **18**, 191; Cohn, W. E., Volkin, E. *Ann. Rev. Biochem.* 1957, **26**, 491; Heppel, L. A., Rubinowitz, J. C. *ibid.* 1958, **27**, 613; Hartman, S. C., Buchanan, J. M. *ibid.* 1959, **28**, 365.
7. Rich, A. N.Y. Academy of Sciences, special publication, 1957, no. 5, p. 186; *Biochim. biophys. acta*, 1958, **29**, 502.

sugar moieties, the bases being adenine, guanine, cytosine, and thymine, while the sugar was desoxyribose. The polymerisation can be represented as:



This synthesis took place only in the presence of some already polymerised material such as desoxyribonucleic acid (usually called the primer), and, after painstaking purification of his enzymes, Kornberg showed that the amount of polymeric material at the end of his experiment was clearly greater than the amount of primer he had started with. Here again, the product was chemically, physically, and enzymically indistinguishable from natural desoxyribonucleic acid.

Protein synthesis is widely thought to be controlled by the genic material of the cell, desoxyribonucleic acid, acting through the ribonucleic acid, and it seems likely that the order in which the four common bases are arranged in the ribonucleic acid must be dictated by the genic material, and that the order specifies, in some form of code, the order in which the various natural aminoacids are built into new protein. Investigations in this fascinating field have been handicapped by the difficulty of isolating undegraded nucleic acids (especially the ribonucleic acids) from the cell, but, now that the work of Ochoa and Kornberg has made available similar polymers made under controlled and reproducible conditions, progress in the mechanism of protein synthesis, and its relation to normal and abnormal metabolism, seems more possible.

GONORRHŒA

AT its first meeting, in January, 1948, the W.H.O. Expert Committee on Venereal Diseases recommended that "international V.D. activities should place major emphasis upon the detection and treatment of early syphilis", remarking that "antibiotic therapy appears to have transformed gonorrhœa from a disease of great chronicity with frequent recurrences, with great tendency to troublesome complications and protracted disability to an infection readily amenable to treatment and with almost complete freedom from complications or tendency to relapse." At its fifth meeting, held in Geneva last month, the committee was presented with figures showing that in 22 countries the annual number of cases of gonorrhœa since 1950 had fallen in only 4, had stayed stationary in 2, and had risen in 16.

Though there seems to be ample evidence that penicillin has been "losing its punch" against certain strains of gonococci, the great majority of infections still respond to generous treatment: the recent worsening of results in some parts of the United Kingdom has not been matched in the United States, where for some years now gonorrhœa has been treated with penicillin in large enough dosage to abort a hypothetical incubating syphilitic infection.

Despite the rise in new cases—and in this country it has been considerable—there is still no evidence of an increase in those crippling complications which made gonorrhœa such a serious public-health problem in the days before specific treatment was feasible. There is, however, no guarantee that such an increase will not occur; and the committee considers that the whole question of gonorrhœa, particularly its diagnosis and treatment, should be taken up internationally by the creation of a W.H.O. gonococcus centre to collaborate with national laboratories throughout the world.

Penicillin, though it has been outstandingly successful in the control of the non-venereal treponematoses, and indeed of the venereal type, has on the whole had a disappointing impact on the incidence of gonorrhœa. This is largely due to faith in one-shot treatment, with failure to recognise that infectious latency, especially in women, is still a feature of the disease. The diagnosis of gonorrhœa in its latent stages is difficult, and the traditional stained films and cultures are no less imperfect for this purpose than they always have been.

LONG-TERM PROGNOSIS IN EPILEPSY

THOSE who undertake the long-term care of epileptic patients know that the frequency of their attacks may vary widely from time to time in an unpredictable and seemingly causeless manner. This greatly increases the difficulty of assessing the results of treatment and emphasises the need for long-term surveys. The effects of surgical treatment are best evaluated when a post-operative period of at least five years can be compared with a similar time before operation.

This spontaneous variation may also give rise to a healthy scepticism about medical treatment. Thus a patient may have a number of fits in childhood or adolescence. He is put on to an anticonvulsant regime, and in a few weeks or months the attacks largely cease. The regime is continued with apparent success; but in the fifth or sixth decade, perhaps with evidence of mild cerebrovascular change, or earlier with no apparent precipitating factors, the attacks recur. What evidence have we that in the intervening years the anticonvulsant treatment has been responsible for the absence of fits? Why should it not have been due to the spontaneous variation which we know occurs? Since both clinical and electrical evidence suggest that epileptic firing is episodic, we must assume that medical therapy is a somewhat blunderbuss affair; and that we should try to discover what factors are likely to initiate or enhance such firing, and then, if they are unavoidable, to apply treatment at times of risk.

This problem has led some physicians to try a periodic reduction of drugs to see whether the frequency of attacks is affected. The majority, however, prefer not to alter a regime on which the patient is having few or no fits. When anticonvulsants are *abruptly* stopped, attacks may be induced which would not have occurred if the brain had never been subjected to the drugs. Nevertheless, there is something to be said for periodic gradual reduction of drugs. After all, no drug should be exhibited unless it is producing the effect for which it is intended; and the known and clinically overt hazards of protracted

treatment with anticonvulsants are not negligible: the subliminal effects on cerebral efficiency are largely unassessed; and when patients themselves mention possible symptoms they are usually dismissed as psychogenic.

With these questions in mind Strobos [1] observed the results of medical treatment in 228 patients with "idiopathic" epilepsy for periods of from two to fifteen years. 86 were completely controlled; in 41 of these an attempt was made to reduce medication, but 19 had a recurrence of attacks. Merritt [2] referred briefly to similar findings in 85 cases of patients with completely controlled attacks who had their drugs gradually reduced. He did not mention the period of observation, but no less than 29 remained seizure-free when off all medication. Undoubtedly detailed reassessment of medical therapy would be of value; and we should seek to define the effectiveness of the various medical treatments in terms of decades rather than years. The opportunity could also be taken for renewed observations on the "natural history" of epilepsy.

COMPARATIVE SUICIDE STATISTICS

THE incidence of suicide has increased in most countries since the late war, and, with the decrease in the death-rate from other causes, suicide now accounts for a higher proportion of deaths, especially among young and middle-aged people. A World Health Organisation publication [3] giving comprehensive statistics on mortality from suicide in various countries drew attention to the comparatively high rate in Denmark; and Dreyer [4] has now examined the Danish figures from 1835. A hundred years ago the crude suicide-rate in that country was higher for males than it is now, and it was about the same for females. The Danish suicide-rate in the 19th century was among the highest in Europe, and Denmark is still near the head of the list. For males, the Danish suicide-rate at the turn of the century was equalled only by Switzerland (about 40 per 100,000 population). The Danish male suicide-rate decreased during the first decade of this century and, as in most other countries, it decreased still further during the first world war, rising thereafter though not to its 1900 level. In the 1939–45 war the rates in males decreased at first in most countries; but in the occupied countries considered (Norway, the Netherlands, Denmark, Finland, and Belgium) the rates either increased or were irregular towards the end of the war. There was also a slight rise in male suicide-rates from 1942 onwards in England and Wales. After the war the suicide-rate among males in Denmark rose to 32 per 100,000, at which level it remains. The suicide-rate among females in Denmark began to rise in 1928, and it rose still more during the 1939–45 war (from 10 per 100,000 in 1939 to 24 per 100,000 in 1945). The sex ratio for suicide in Denmark and most European countries was 3 or 4 males to 1 female in the latter part of the 19th century, but in Denmark the increased number of female suicides has kept the ratio at about 2 to 1 since 1950.

Dreyer analyses the Danish age-specific suicide death-rate, comparing it with the corresponding rate for England and Wales. Swinscow [5] found that in England and Wales suicides under the age of 55 included a relatively high proportion of females, but the Danish figures show no such trend, except in the late war; and, whereas Swinscow found that the proportion of all suicides accounted for by the younger age-groups was falling, Dreyer finds that the proportion (except during and just after the war) remains more or less constant.

In addition to sex and age, Dreyer considers season and method. A table of seasonal distribution from 1835 to 1955 shows a peak rate in the early summer months (May to July) and a smaller peak in the autumn in most periods; but these seasonal variations have been less pronounced in recent decades. Seasonal graphs given by Swinscow for England and Wales for the three decades from 1921 show a similar peak slightly earlier in the year, with a tendency to higher rates in the end months but a narrower range of fluctuation. As regards method, Dreyer shows that since the 1940s male Danish suicides have not changed their methods but that there has been a considerable fall in the percentage of females using poison with a corresponding increase in drowning and hanging.

1. Strobos, R. R. J. *A.M.A. Arch. Neurol.* 1959, **1**, 216.
2. Merritt, H. H. *Brit. med. J.* 1958, i, 666.
3. *Epidem. vit. Stat. Rep. World Hlth Org.* 1956, **9**, no. 4.
4. Dreyer, K. *Danish med. Bull.* 1959, **6**, 65, 75.
5. Swinscow, D. *Brit. med. J.* 1951, i, 1417.

FORMATION OF RENAL CALCULI

THE administration of acetazolamide to rats has been shown to decrease the urinary excretion of citrate and to promote deposition of calcium in the kidneys.[1] Albright et al.[2] had previously used the solvent effect of citrate on calcium to attack urinary calculi in vivo by lavage of the bladder or renal pelvis with buffered citrate solutions. Absence of citrate in the urine of patients with calculi was first noted by Boothby and Adams [3]; and a similar observation was later reported by others.[4 5] Shorr [6] considered that the absence of citrate from the urine, with consequent failure to hold calcium in solution, was an ætiological factor in the production of calcium stones. Since in women excretion of citrate increases during ovulation and in either sex a similar increase can be obtained by administration of œstrogen, Shorr suggested that this hormone might be administered for treatment of patients with urinary stones; and Robinson [7] reviewed this treatment with approval. Conway et al.,[8] on the other hand, failed to confirm that deficient renal excretion of citrate was important in the formation of renal calculi. They believed that any gross diminution of urinary citrate was due simply to infection of the urinary tract. Experiments in vitro confirmed that the organisms commonly present in infected urine destroyed citrate.

Nevertheless, the view that calculi are formed because of a deficiency of some substance, normally present in the urine, which binds calcium to form a soluble complex is an attractive one. It would explain the "supersaturation" of the urine with calcium—a concept which has been generally accepted, and which has been upheld by solubility studies.[9 10] Dr. Mary McGeown,[11] of Belfast, has now brought forward evidence which suggests that the chelating agents are the urinary aminoacids. She examined twenty-four-hour collections of urine from 110 patients with calcareous renal calculi and from 29 healthy people. The mean urinary aminoacid nitrogen in the control group was 322·9 mg. and in the patients 235·0 mg. per twenty-four hours. Only 2 of the 29 controls, compared with 44 of the 110 patients excreted less than 200 mg. No difference in

1. Harrison, H. E., Harrison, H. C. *J. clin. Invest.* 1955, **34**, 1662. See *Lancet*, 1957, ii, 630.
2. Albright, F., Sulkowitch, H. W., Chute, R. *J. Amer. med. Ass.* 1939, **113**, 2049.
3. Boothby, W. N., Adams, N. *Amer. J. Physiol.* 1934, **107**, 471.
4. Kissin, B., Locks, M. O. *Proc. Soc. exp. Biol., N.Y.* 1941, **46**, 216.
5. Scott, W. W., Huggins, C., Selman, B. C. *J. Urol.* 1943, **50**, 202.
6. Shorr, E. *ibid.* 1945, **53**, 507.
7. Robinson, R. H. O. B. *Proc. R. Soc. Med.* 1947, **40**, 201.
8. Conway, N. S., Maitland, A. I. L., Rennie, J. B. *Brit. J. Urol.* 1949, **21**, 30.
9. Vermeulen, C. W., Lyon, E. S., Miller, G. H. *J. Urol.* 1958, **79**, 596.
10. Yarbro, C. *ibid.* 1958, **80**, 158.
11. McGeown, M. G. *Clin. Sci.* 1959, **18**, 185.

aminoacid nitrogen excretion emerged when the urines of the patients were subdivided according to whether they were sterile (53) or infected (57). Means [12] remarked on the fact that in thyrotoxicosis hypercalcuria with gross depletion of the skeleton may occur, and yet calculi are not associated with this disease. Nor do calculi develop in Fanconi's syndrome, in which there is excessive excretion of both calcium and aminoacids.[13] Lehmann and Pollak [14 15] at Cambridge found in in-vitro experiments that aminoacids increased the solubility of calcium and magnesium phosphates. The most effective aminoacids proved to be cysteine, glycine, glutamic acid, arginine, citrulline, alanine, ornithine, lysine, and leucine; cysteine was about twice as effective as glycine and lysine, and thiolacetic acid was also effective. The work of Lehmann and Pollak suggested that cystine, on the other hand, might form an insoluble complex with calcium salts; and Dr. McGeown found that 31% of the calculus patients had an increased excretion of cystine. In some of the patients the excessive excretion of cystine may have been due to tubular damage, but many of them had no evidence of impaired distal tubular function. Damage to the proximal tubules is seldom accompanied by excessive excretion of aminoacids. The excessive excretion of cystine seen by Dr. McGeown seems therefore to represent a specific defect in the handling of one aminoacid.

The Cambridge workers studied the effect of protein intake on the absorption of calcium and magnesium,[16 17] and concluded that very little calcium would be absorbed if the diet contained no protein or aminoacids. Mellanby [18] had previously observed that casein had some antirachitic effect over and above that due to its calcium content, and McCance et al.[16] pointed to the interesting position of meat in the diet: this substance, itself rather poor in calcium, may so promote calcium absorption by providing a plentiful supply of aminoacids that it becomes the equivalent of a food rich in calcium.[18] Lehmann [19] remarked that the two organs most commonly showing pathological calcium deposits in their excretory channels are liver and kidney. Besides removing water from biological fluids, these are particularly rich in aminoacid oxidases. In model experiments he showed calcium deposition when water-soluble enzyme from pig's kidney was added to a supersaturated solution of calcium phosphate in 20% alanine.[20] Such a high concentration of aminoacid is hardly physiological, and conditions in vivo might have been imitated more closely by using a much lower concentration of aminoacid and by observing precipitation of calcium over a period of days rather than over a period of an hour. Under the conditions chosen there was a considerable time lag between deamination of alanine and precipitation of calcium, and deposition of calcium continued for some time after the enzyme had been inactivated. The chelating effect of protein and its breakdown products has been held responsible for decalcification of teeth.[21]

Not all of the 110 patients examined by Dr. McGeown showed a lowered urinary aminoacid excretion; possibly her observations should be considered with others on the effect of citrate on the solubility of calcium. Furthermore her work was concerned with single twenty-four-hour collections of urine. Repeated tests might show an overall deficiency of urinary aminoacids.

12. Means, J. H. The Thyroid and its Diseases; p. 330. London, 1948.
13. Dent, C. E., Harris, H. *J. Bone Jt Surg.* 1956, **38B**, 204.
14. Lehmann, H., Pollak, L. *J. Physiol.* 1942, **100**, 17P.
15. Lehmann. H., Pollak, L. *Biochem. J.* 1942, **36**, 672.
16. McCance, R. A., Widdowson, E. M., Lehmann, H. *Biochem. J.* 1942, **36**, 686.
17. Hall, T. C., Lehmann, H. *ibid.* 1944, **38**, 117.
18. Mellanby, E. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1925, no. 93.
19. Lehmann, H. Biochemical Society Symposia, 1948, no. 1.
20. Lehmann, H. *Nature, Lond.* 1942, **150**, 603.
21. Schatz, A., Karlson, K. E., Martin, J. J., Schatz, V. *Ann. Dentist.* 1957, **16**, 37.

WILLIAM HARVEY, NEUROLOGIST

William Harvey's place among the immortals of medicine was secured by his description of the circulation of the blood; but he made other important, though less revolutionary, observations. He devoted much time to obstetrics and gynæcology; and, as Sir Russell Brain pointed out in his Harveian Oration, delivered to the Royal College of Physicians of London on Oct. 19, he was no mean neurologist. He made no major original observations concerning the functioning of the nervous system, nor were his descriptions of nervous disease as comprehensive and definitive as those of later physicians; but scattered through his writings are many fragmentary observations which attest to his clinical acumen, to his perseverance, and to his spirit of critical inquiry. From Harvey's *De Motu Locali Animalium*,[1] translated by Dr. Gweneth Whitteridge and now published for the first time, and from the *De generatione* [2] and *Prelectiones*,[3] Sir Russell had collected material showing that Harvey, for the times in which he lived, was exceptionally interested in the functions of the nervous system and had a remarkable grasp of the problems of clinical neurology.

Clearly Harvey, unlike his contemporaries, believed that the fleshy part of a muscle was particularly concerned with contraction; and from his study of insects, birds, and animals he distinguished between tonic or sustained contractions (anticipating in a sense the concept of postural tone) and the intermittent contractions concerned with movement or propulsion. He also made some acute observations on the role of synergists and antagonists in muscular activity. In considering the organisation of movement he decried those theories which demanded a motivation from the soul, and distinguished clearly between movements that were largely autonomous and those controlled by the will. His conclusions on the significance of involuntary movements were also remarkably modern in many respects, and he was aware that the organisation of movement depended largely on forms of sensation which did not enter consciousness. Harvey's experience of cases of apoplexy and of other brain diseases convinced him that the cerebral substance was itself all-important, despite the contemporary view that the spirits or humours within the ventricles controlled nervous activity. Of Harvey's clinical observations—his descriptions of pupillary changes, of exophthalmos, of abnormalities of gait, of muscular fasciculation, of hysteria, and of a probable case of syringomyelia—Sir Russell had much more to say. These amply sustain Sir Russell's view that Harvey was by no means a physician of limited interest, but that he belonged to that rare genus of geniuses—the comprehensive man.

Prof. A. L. HODGKIN and Prof. R. MILNES WALKER have been appointed members of the Medical Research Council in succession to Prof. R. C. GARRY and Mr. H. J. SEDDON, who are retiring. Sir HUGH LINSTEAD has been appointed as the House of Commons member of the Council in succession to the late RICHARD FORT.

1. Harvey, W. De Motu Locali Animalium. Edited and translated by G. Whitteridge. Cambridge, 1959. See *Lancet*, 1955, i, 971.
2. Harvey, W. Exercitationes de Generatione Animalium. London, 1847.
3. Harvey, W. Prelectiones Anatomiæ Universalis. London, 1886.

Public Health

LEUKÆMIA AND GEOGRAPHY

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ALL over the world, wherever records have been kept, the incidence of leukæmia has been apparently increasing since early in the present century. In Britain the crude death-rate from leukæmia in England and Wales in 1920 was 1·1 per 100,000 population and by 1957 the rate had risen to 5·3.

Two recent statistical studies (Hewitt 1955, Registrar General 1957) have shown that the incidence of leukæmia is higher in males than in females and it affects children and the aged more than other age-groups. Prosperous areas suffer more than areas with a low standard of living. Thus northern U.S.A. has a higher leukæmia death-rate than the south, but in Britain the southern counties have a higher death-rate than the less prosperous north. Nevertheless it is not prosperity as such which causes leukæmia, and Hewitt, after discussing various possibilities, suggests that the real factor is increased exposure to radiation.

The picture of leukæmia incidence is not static, and this paper is an attempt to define the changing pattern and interpret it.

The 1957 figures showed that the leukæmia death-rate for Caernarvonshire had reached its highest point ever, and the rate had been rising fairly rapidly. It occurred to me that other areas might have had a similar experience, and they would be of particular interest if they resembled Caernarvonshire in topography and employment pattern. For such a comparison the standard regions used by the Registrar General were too large, and I decided therefore to calculate rates for all geographical counties in England and Wales.

COUNTIES COMPARED

Unfortunately figures were not available for local-authority areas before 1950, so only eight years could be studied, and this was too short a period to provide figures on which unassailable conclusions could be based, but nevertheless the comparison seemed worth pursuing. The figures were divided into two four-year periods: 1950–53 and 1954–57, and crude death-rates from leukæmia were calculated for each geographical county, with its enclosed county boroughs. The rates were calculated per 100,000 population, using the average population in each four-year period. Since the main object was to examine the change in death-rate by contrasting the two periods, standardised death-rates were unnecessary; but in point of fact the distribution revealed using crude rates is very similar to that obtained with standardised rates by the Registrar General (1958).

The full results are shown in the accompanying table and illustrated in figs. 1 and 2.

During both periods the south of England and the London area had rates above the average. In the second period the incidence rose in the North, but the concentration of high incidence counties into the south became more pronounced because certain mainly rural counties (Shropshire, Huntingdonshire, Cheshire, Bedfordshire, Radnorshire, Cardiganshire, and Carmarthenshire) moved into a state of lower incidence.

There remained, however, some high-incidence counties outside the southern aggregation—Herefordshire, Derbyshire, Durham, and three in North Wales. Herefordshire and Derbyshire were high-incidence counties during the first period (and their appearance there is not easy to explain), but Durham and Caernarvonshire appear in the high-incidence group for the first time. To try to suggest a reason for this, those counties were studied in which leukæmia death-rates had increased rapidly.

TWO PERIODS CONTRASTED

Over England and Wales as a whole the leukæmia death-rate increased by 13% in the second four-year period compared with the first. Some counties suffered substantially more than this, and fig. 3 shows those counties where the rate increased by over 30% and by over 50%.

At the 30% level are Cambridgeshire, Breconshire, and Durham. Cambridgeshire seems to be in a different category from the other two in that it is contiguous with the high-incidence area round London as well as with low-incidence Lincolnshire. Perhaps its presence in the 30% group is due to the exceptional interest in hæmatology in the university town.

Durham and Breconshire, however, may be regarded as reflecting in a less dramatic form the experiences of neighbouring counties which have sustained an even

LEUKÆMIA DEATHS IN COUNTIES

County	1950–53 No. of deaths	1950–53 Rate per 100,000 population	1954–57 No. of deaths	1954–57 Rate per 100,000 population	Increase in rate
London	719	5·3	766	5·8	9%
Bedfordshire	64	5·0	49	3·7	..
Berkshire	72	4·3	90	5·0	16%
Buckinghamshire	83	5·3	105	6·3	19%
Cambridgeshire (including Isle of Ely)	39	3·7	56	5·2	39%
Cheshire	228	4·53	228	4·4	..
Cornwall	71	5·2	69	5·0	..
Cumberland	35	3·1	56	4·9	59%
Derbyshire	157	4·7	175	5·2	9%
Devon	157	4·9	182	5·6	15%
Dorset	78	6·6	66	5·4	..
Durham	228	3·7	304	5·1	38%
Essex	374	4·55	494	5·7	26%
Gloucester	145	3·8	171	4·4	16%
Hampshire (with Isle of Wight)	306	5·8	306	5·6	..
Hereford	31	6·1	35	6·8	13%
Hertfordshire	91	3·6	151	4·3	20%
Huntingdonshire	16	5·8	6	2·0	..
Kent	342	5·4	419	6·5	19%
Lancashire	829	4·1	989	4·8	20%
Leicestershire	102	4·0	130	5·0	25%
Lincolnshire	116	4·1	114	4·0	..
Middlesex	414	4·6	484	5·4	18%
Norfolk	108	4·9	102	4·6	..
Northamptonshire with Soke of Peterborough and Rutland *	68	3·8	68	3·7	..
Northumberland	119	3·7	150	4·7	25%
Nottinghamshire	139	4·1	164	4·7	15%
Oxfordshire	62	5·4	73	6·1	14%
Shropshire	64	5·4	49	4·1	..
Somerset	107	4·53	112	4·9	8%
Staffordshire	267	4·1	305	4·6	12%
Suffolk	78	4·3	88	4·9	13%
Surrey	351	5·4	395	6·0	10%
Sussex	217	5·7	235	6·0	5%
Warwickshire	314	4·2	354	4·6	10%
Westmorland	5	1·8	12	4·5	140%
Wiltshire	69	4·4	90	5·0	13%
Worcestershire	92	4·4	105	4·8	11%
Yorkshire	612	4·1	714	4·8	19%
Anglesey	7	3·5	5	2·4	..
Breconshire	8	3·5	11	4·9	38%
Caernarvonshire	15	3·1	27	5·5	80%
Cardiganshire	11	5·1	6	2·8	..
Carmarthenshire	31	4·53	28	4·1	..
Denbighshire	33	4·8	36	5·3	9%
Flintshire	32	5·5	27	4·6	..
Glamorganshire	198	4·1	199	4·1	..
Merionethshire	4	2·5	4	2·5	..
Monmouthshire	53	3·1	87	5·1	65%
Montgomeryshire	11	6·1	18	10·0	65%
Pembrokeshire	12	3·3	15	4·0	25%
Radnorshire	6	7·5	1	1·3	..
England and Wales		4·5		5·1	13%

* Rutland had 2 cases in the 8 years, both in 1956.

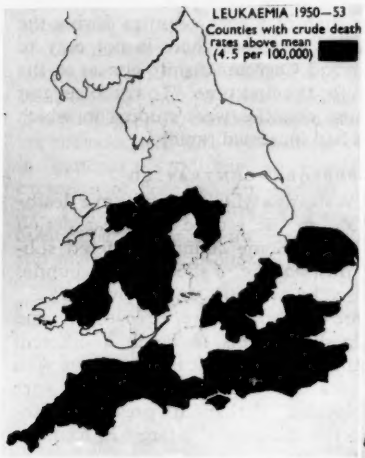

Fig. 1—Counties with crude leukæmia death-rates above mean, 1950–53.

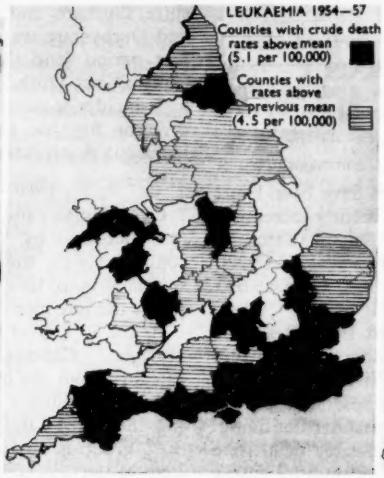
LEUKAEMIA 1954–57
Counties with crude death rates above mean (5.1 per 100,000)
Counties with rates above previous mean (4.5 per 100,000)

Fig. 2—Counties with crude leukæmia death-rates above mean and previous mean, 1954–57.

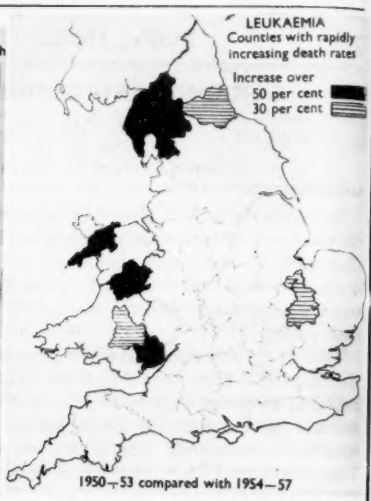

Fig. 3—Counties with rapidly increasing leukæmia death-rates.

bigger increase. At the 50% level are the five black counties in fig. 3—Cumberland, Montgomery, Westmorland, Caernarvon, and Monmouth. The first four named are strikingly similar topographically. All are mountainous areas of high rainfall on or near the western coast. Monmouthshire does not quite fit into the pattern, although much of it is also mountainous.

These counties (with one exception) used to have very low rates. So that in spite of the rapid increases, they do not all show up as high incidence areas on the second map (fig. 2). Caernarvon, however, has now arrived in this category, and Montgomery, which had a high incidence in the first period, now has a rate of 10 per 100,000 over the second four-year period—the highest rate of any county in England or Wales.

Cumberland and Westmorland, in spite of the increases, are only now approaching the national mean considered on the four-year basis. The increase has been consistent since 1954, however, and in 1957 the rates in both counties were above the average.

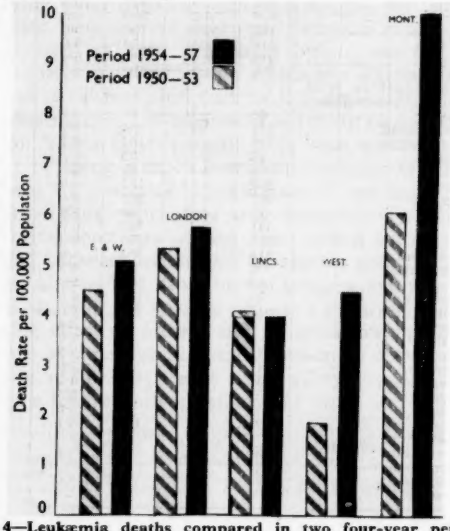

Fig. 4—Leukæmia deaths compared in two four-year periods. E. & W., England and Wales; West., Westmorland; Mont., Montgomery.

ATTEMPTED CLASSIFICATION

It is hard to fit all the counties into a system, but four types of experience can be picked out, and these are illustrated in fig. 4.

(*a*) London is a good example of the experience of many counties of the south of England. It is a high-incidence area and during the past eight years it has suffered a moderate rise in death-rate—7%.

(*b*) Many rural areas (but not south of London) enjoy a low incidence of leukæmia. In most of them the death-rates have remained more or less constant—e.g., Lincolnshire.

(*c*) Certain rural areas in the West used to be areas of very low incidence. Some of them, after a dramatic increase in recent years, are now near the national mean or above it—e.g., Westmorland.

(*d*) Montgomery is a high-incidence rural county which has also sustained a rapid increase in death-rate—the only example in this class.

DISCUSSION

The high incidence in the prosperous south and the lower rates in the north and in most rural areas conform to the normal pattern. But since 1954 the four key counties have been Cumberland, Westmorland, Caernarvon, and Montgomery. They are all poor rural counties and have nothing in common with the lush south or with congested connurbations. Why should they experience a sudden rise in leukæmia death-rates?

The diagnosis of leukæmia is often difficult (Witts 1957), and a low incidence may be, in part, due to underdiagnosis, but a sudden rise like this is very unlikely to be due only to improved case-finding because that would imply that the standard of medical services has suddenly risen in four separate areas quite independently. The rise is also, for the same reason, equally unlikely to be due to increased use of therapeutic or diagnostic radiology.

The following explanation may partly meet these difficulties.

Radioactive Fallout

Whenever a thermonuclear device is exploded radioactive substances are released and ascend into the stratosphere. Most of the substances lose their radioactivity rapidly, but some such as plutonium 239, cæsium 137, and strontium 90 (^{90}Sr) are long-lived and are subsequently deposited on the earth while still active. From the point of view of leukæmia the important element is

^{90}Sr. It was originally estimated that 10% or 20% of the total amount of radioactive debris is deposited each year, but later evidence indicated a more rapid fallout. Areas in the northern hemisphere including the British Isles have deposits three times heavier than the world average (U.N. Scientific Committee 1958), and the amount of deposition of radioactive dust varies also within the United Kingdom, so that mountain areas of high rainfall show high levels of ^{90}Sr in soil and vegetation. Bryant et al. (1958a) found that the soil in Cwmystwyth near the Cardiganshire–Montgomery border at a height of 1200 ft. contains three times as much ^{90}Sr as soil in Cambridgeshire, and the figures for Borrowdale in Cumberland were even higher.

This high level of radiostrontium deposition, especially when combined with a low soil calcium, leads to high figures for ^{90}Sr in vegetables, milk, and animal flesh. Thus milk from a special area in Cardiganshire during the period March–December, 1958, contained 28·4 strontium units (S.U.) * and that from Cumberland 21·1 S.U., compared with a countrywide mean of 6·97; and according to an estimate of the Agricultural Research Council (1959) the diets of those living in areas of high fallout may conceivably contain 23 S.U. or more compared with the national mean of 5·9 S.U.

Since strontium follows the path of calcium in the body it is concentrated in bones; and during 1957 about 100 samples of human bone were examined for radiostrontium in the Atomic Energy Research Establishment (Bryant et al. 1958c). The mean figure for strontium in children's bone was 1·2 S.U., and 2·4 S.U. was recorded in one case from Wales and 3·2 in a case from Scotland. Higher figures may have been reached in some individuals in regions of high strontium fallout, and in an area largely self-supporting for foodstuffs, like many country districts, a figure of 10 units may have now been reached in some inhabitants.

Critical Level of Radiation to Bone

It is not known whether there is a threshold level in bone below which no harmful effects from radiation will occur, but it is widely held that 10 S.U. is a " safe " level. This amount of strontium would give an estimated marrow dose of only 30 millirem per annum, which is less than that given by the natural radium in bone (37 millirem) or by background radiation (80 millirem) (Medical Research Council 1956).

Assuming that there is no threshold the effect expected from this amount of radiation would be well-nigh undetectable according to current theories. It has been suggested by Court Brown and Doll (1957) that 1r might produce one case of leukæmia per million population per year, and the figure suggested by the United Nations Scientific Committee (1958) for the same dose is 1·5 cases per million. On this scale the addition of 0·03r would be expected to cause only 1 or 1·5 additional cases of leukæmia per 33 million. The actual increases noted are of the order of 2 per 100,000 or about 600 times the expected number. But the exposure of millions of people to artificial internal radiation is an experiment on a scale impossible in the laboratory, so one should not be too surprised if some of the effects are unpredicted.

Type of Leukæmia

The myeloid type of leukæmia was the form associated with the atom-bomb explosions at Hiroshima and Nagasaki (Witts 1957). Figures have not yet been published for the types of leukæmia in each county, so no general investigation of this point was possible, but figures for Caernarvonshire were available, and in the four years 1954–57 there were 16 deaths (59%) due to myeloid leukæmia. For England and Wales as a whole, the figure was 45%.

Conclusion

Certain facts support the suggestion that the rapidly rising leukæmia death-rate in some western counties is associated with ingestion of ^{90}Sr. Within the next two or three years additional statistical data will enable the possibility to be examined more closely. If ^{90}Sr is increasing, leukæmia mortality will continue to rise in the next few years in Cumberland, Westmorland, Caernarvon, and Montgomery, and the rise will next affect Merioneth and Cardigan. Later perhaps Cornwall and Devon will become involved, and thereafter the figures for the rest of England and Wales will start rising more steeply.

Two steps might throw light on the question: the publication of more detailed statistics of the type of leukæmia deaths in all areas; and the direct examination of many more samples of human bone for ^{90}Sr, especially of bone from patients dying of leukæmia.

Summary

In five counties (Cumberland, Westmorland, Caernarvon, Montgomery, and Monmouth) leukæmia death-rates have been rising rapidly, the rise being over 50% in two successive four-year periods.

The rates prevailing in these four counties were all above the mean for England and Wales in 1957, but taken on a four-year basis only Montgomery has an outstandingly high death-rate and is the highest in the two countries (10 per 100,000).

A possible cause is radiostrontium fallout, and more research is indicated, especially into the levels of radiostrontium in bones of leukæmia patients from mountainous western counties.

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* 1 strontium unit = 1 micromicrocurie of strontium per g. of calcium.

Vaccination against Influenza

The Ministry of Health reports that it is receiving from general practitioners and the public a considerable number of inquiries about vaccination against influenza. A Ministry statement says:

" The decision whether or not vaccination is desirable in an individual case must rest with the general practitioner. But from the information and expert advice that are available to the Ministry there is at present no indication of the likelihood of a major epidemic of influenza in this country during the coming winter. Moreover it is not possible to identify in advance the particular strain of influenza virus that would cause such an epidemic if one should occur.

" For these reasons the Ministry are not making any special arrangements for vaccination against influenza. Present circumstances are quite different from what they were in the autumn of 1957."

Special Articles

DIRECT ARTIFICIAL RESPIRATION
TRAINING WITH THE BROOK AIRWAY

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SEVERE hypoxia is the commonest precursor of death in fatal accidents, in postpartum asphyxia in infants, during anæsthetic difficulties, in fires and military disasters, in home and industrial accidents, and in acute diseases. Even so, there are few physicians, nurses, or rescue-workers who are well trained in the prompt restoration of a clear airway in an unconscious injured man with airway obstruction, or in a seriously ill patient. This treatment alone can save countless victims who die every year (Dobkin et al. 1957, Dill 1958).

A great deal of investigation has shown that the manual methods of artificial respiration do not provide an adequate clear airway, and are therefore never as efficient as the direct oral intermittent insufflation of expired air by a rescuer (Gordon et al. 1958, Safar et al. 1958). The direct mouth-to-mouth method is by far the best and most efficient method in an emergency, and should be taught first because it is the only method that is always available. Most teachers, however, find it unsatisfactory to demonstrate because of æsthetic objections, the fear of infection, and the difficulty in demonstrating it to lay people and rescue teams, even with trained subjects (Safar and McMahon 1958).

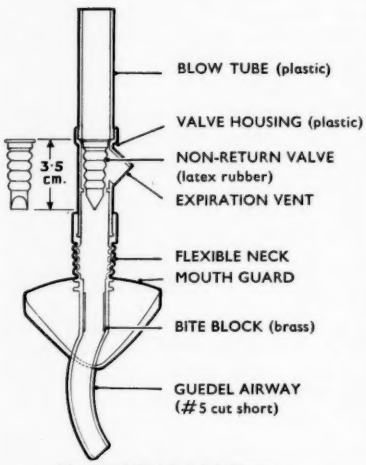


Fig. 1.—The Brook Airway

Artificial and Mechanical Resuscitators

Various devices have been designed to avoid the use of direct mouth-to-mouth resuscitation, but many of these are still unsatisfactory: it takes time to train lay people in their proper use; if improperly applied they can aggravate the conditions which they are meant to treat; they are not universally applicable; and some are expensive to purchase and maintain. Several such special devices are now available for direct artificial respiration. None of these are easy to use by the layman, and the simplest do not eliminate the danger of infection to the rescuer (Safar and McMahon 1958, Hingson 1958, Lucas and Whitcher 1958, Ruben 1959, Lee and Tarrow 1959, Ruben et al. 1959).

An oral airway has been developed at the University of Saskatchewan, known as the Brook airway. It is cheap, simple to clean and maintain, very easy to use even after a brief demonstration, and effective in a wide variety of emergencies. This airway (fig. 1) consists of three main components:

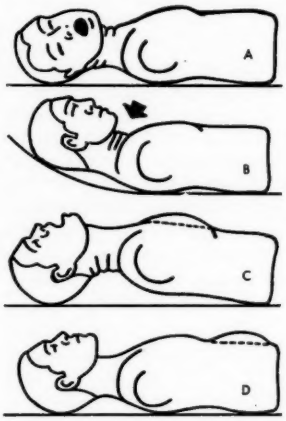
1. A clear vinyl plastic Guedel airway with a flexible neck containing a brass bite-block and a mouth guard. The oral portion of the airway has been cut short. This airway is made for adults, but is also to be had in smaller sizes for children. Its use is not recommended for infants. Correct introduction provides a clear airway and seals the mouth so that air passes into the lungs without leakage.
2. A vinyl plastic unidirectional valve assembly that consists of two parts: a rigid plastic housing, 5 cm. long, which contains a snug-fitting, slightly tapered corrugated latex-rubber valve, which is removable for cleansing or replacement.
3. A disposable rigid vinyl plastic blow tube 6 cm. in length.

Expired air or oxygen blown into the tube encounters a resistance in the valve of less than 0·5 cm. of water, even at very low flow-rates. Moreover, no air entering the blow tube can leak around the valve through the expiratory vent. Return flow of expired air cannot enter the valve, and it escapes from the vent when the pressure exceeds about 1·5 cm. of water. The components of the airway can be taken apart easily in a moment. If the victim's pharynx must be cleared by suction, the blow tube and valve assembly can be detached and a suction catheter (up to size 18 French) may be passed into the pharynx with ease. The oral portion of the airway is long enough to establish a clear airway over the tongue without causing gagging or retching in the conscious patient. This is often an important consideration—for example, when artificial respiration must be carried out in the fully awake victim of an accident in which chest compression prevents air entry into the lungs. It is also important where the lung has collapsed because of a chest injury or rupture of emphysematous bullæ. Even if the victim is semiconscious, the risk of vomiting and aspiration, to which the insertion of an ordinary anæsthetic airway would predispose, is negligible with this device.

Fig. 2.—Airway-passage model.
Note that the hinges allow extension and flexion of the head on the neck, opening and shutting of the mouth, depression or drawing the lower jaw forward.

Instruction

The proper use of any device in an emergency depends on well-planned training. Since among doctors, anæs-



A — The head is turned to the side to remove secretions from the mouth and pharynx.

B — Elevating the head on a pillow causes flexion of the neck and partial airway obstruction.

C — The airway passage is open when the head is extended—indicated by expansion of the chest when air is blown into the "mouth" (chest deflates as the air is "exhaled").

D — With head in neutral position air blown into "mouth" may enter stomach. To remove apply pressure on "epigastrium".

Fig. 3.—The plastic mannikin.

Head upright, partial obstruction
Head down, complete obstruction
After clearing pharynx of mucus tilt head into sniffing position
Grasp chin and mouth-guard with one hand, pinch nostrils with the other hand.
Elevate chin and insert airway
Rotate airway into position
Take a deep breath, blow through airway till chest rises, listen to exhalation, and take another deep breath. Reinflate lungs 10–15 times a minute.

Fig. 4—The care of the unconscious: direct artificial respiration.

thetists have most experience in the management of airway complications, they should take the lead in every hospital and in every community in setting up courses of instruction in artificial respiration by the most efficient method known.

Following the lead by Dr. Safar, Dr. Elam, Dr. Henning Ruben, and the New York Society of Anesthesiologists, we have devised such a course for the lay public and rescue teams. This may be given in a classroom or on television, and the necessary knowledge can be imparted in an hour. Instruction is verbal, visual, and mechanical.

Verbal

A brief historical description of artificial respiration is given, pointing out the advantages and drawbacks of the various methods that have been used (Dobkin 1959). This is illustrated with appropriate slides (10 minutes).

Visual

A 16 mm. motion picture in colour is shown (30 minutes).* The comparative effectiveness of the various methods of artificial respiration on an anæsthetised and curarised apnœic subject are demonstrated. The application of direct artificial respiration is then shown in a series of simulated common emergency situations in which prompt resuscitation would be crucial to saving life.

In each of these scenes, the approach and application of the method which is best in the particular circumstances are clearly shown. These scenes include a collision between two cars (sternal injury and respiratory obstruction); a capsised boat (drowning); a child trapped in an abandoned refrigerator (suffocation); an infant covered with a plastic bag (suffocation); a case of barbiturate poisoning; an electrocution on a telephone pole, and on the ground; a choking scene (aspiration); a heart-attack during exertion; and a serious home injury.

The film closes with classroom-type demonstrations which show how a clear airway is established, and how direct artificial respiration is performed.

* Dobkin, A. B., Brook, M. H. *Breath of Life*; produced at the University of Saskatchewan College of Medicine, Saskatoon, Canada.

Mechanical Demonstration with Models

Finally, the students learn the precise technique and can practise without use of human volunteers.

Air-passage model (fig. 2).—This consists of a natural-size section of the head and neck made of 5-ply wood which is hinged at the bottom of the front of the neck and at the occiput to an L-shaped wooden frame. The mouth, nasopharynx, oropharynx, larynx, upper trachea, and upper œsophagus are shown in partial section outlining the relation of the airway to the palate, tongue, mandible, epiglottis, thyroid cartilage, and cervical spine. A set of hinges have been built into the section so that the head may be flexed or extended on the neck, the mouth can be opened and shut, and the lower jaw can be drawn forward or depressed with the attached larynx, thyroid, and trachea. Extension of the head on the neck causes simultaneous forward and downward displacement of the mandible with the attached tongue and marked widening of the oropharyngeal passage.

The plastic mannikin (fig. 3).—This has natural anatomical features of the upper portion of the body with the special internal features of the airway and lungs, œsophagus and stomach. The head can be turned to show the technique for removing foreign material and secretions from the mouth and pharynx. The head can be flexed or extended on the neck to show how these affect the airway during artificial respiration: flexion causes complete occlusion of the airway by the tongue, as is seen in the section. If the nose is not pinched, the large air leak can be shown. Air may enter the " stomach " and can be expelled by epigastric pressure. The mannikin can be cleaned very quickly both externally and internally between demonstrations.

The most efficient method for inserting an artificial airway is shown on the plastic mannikin. Direct artificial respiration (intermittent positive-pressure ventilation) is carried out on the mannikin with the head in the incorrect and the correct position, and similarly when an artificial airway is used. The improved ventilation that follows when the mouth is sealed about the airway and the nostrils are pinched is also shown in order to impress the trainees with the importance of preventing air leaks during direct artificial respiration. The operation of the non-return valve is shown on the airway to emphasise that the expired air from the victim is vented completely to the air without returning to the rescuer.

The demonstrations are followed by personal trial by each trainee on the mannikin using both the mouth-to-mouth method and the mouth-to-airway method. In the latter, each trainee uses his own disposable blow tube so that cross infection is prevented (fig. 4).

I would urge all doctors, particularly those concerned with teaching anæsthetics, to do all they can to promote this type of instruction course. The small amount of effort required to carry out such instruction in classrooms or on television programmes will surely save a great many more victims of serious emergencies than have been saved in the past by the indirect (manual) methods of artificial respiration.

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Congresses

SURGERY

DELEGATES from all over North America and from many other parts of the world gathered in Atlantic City on Sept. 28 to Oct. 2 for the annual clinical congress of the American College of Surgeons, under the presidency of Dr. NEWELL W. PHILPOTT (Montreal).

Control of Infection in Hospitals

Dr. CARL WALTER (Boston, Mass.) and a panel of experts showed how infection may be controlled by such simple expedients as using sterilised mops and flooding the floors with effective disinfectants, then removing the fluid by wet vacuum suction. Air-conditioning and ventilating plants are a hidden vector; and lifts act as pistons, and staircases as chimneys, for bacteria-laden air.

Pitfalls of Biliary Surgery

In this panel discussion it was suggested that the "post-cholecystectomy syndrome" often reflects an incorrect pre-operative diagnosis. At what age should symptomless gall-stones no longer be removed? asked one delegate. The panel believed that one should not wait until the patient was too old. Surgeons, they felt, were the worst offenders. At this, the Moderator asked all those present with unoperated gallstones to stand up: no-one rose. Subsequently 9 surgeons of the 1000-odd present admitted to having had gallstones removed.

Hypothermia

Dr. E. M. BARSAMIAN and others (Boston, Mass.) had impregnated dog hearts with glycerin, dehydrated them to the extent that up to 55% of their water was removed, and then supercooled them to −8°C (freezing-point under these conditions is −9°C). After one hour at this temperature they were transplanted into the neck vessels of a recipient dog, and the heart-beat in them was resumed.

Dr. N. E. SHUMWAY and Dr. R. R. LOWER (San Francisco) had applied local cold to the heart and found that this greatly increased tolerance to anoxia.

Dr. P. A. SALMON and Dr. R. READ (Minneapolis, Minn.) had placed a balloon in the stomach, and irrigated it with ice-cold water through a coaxial out-and-return plastic-tube circuit, over-distension being prevented by the use of a measured, safe amount of fluid. By this device massive gastroduodenal hæmorrhage had been checked in many cases, probably by a local cold response in the gastric blood-vessels.

Arteriography

Dr. JOHN A. WILLIAMS and his colleagues (Boston, Mass.) have devised a simple modification of the Seldinger catheter, for selective arteriography of the aortic branches. The last 2–3 inches (i.e., the tip) is coiled on a former and held in hot water, and on cooling, though this coil can readily be straightened on a guide, and thus easily introduced in the usual way, on removal of the guide the spiral at once reforms and can be approximated closely to the branch orifice concerned. Here, as was shown in glass models by the injection of ink through the catheter, the horizontal inclination of the open tip would result in a dense local deposition of contrast medium and highly selective placing of the injection at any required level in the aorta from the coronary orifices down to the bifurcation.

Dr. E. E. HERTZBERGER and Dr. G. W. SMITH (Augusta, Georgia) showed that the carotid and vertebral arteries can be selectively studied by percutaneous puncture of the subclavian artery in its third part, and the introduction of a nylon guide, then of a polyethylene catheter.

Vascular Surgery

Dr. J. J. MCCAUGHAN, Jr., and Dr. C. D. SCHEIBERT (Memphis, Tenn.) had examined the carotid arteries in 100 consecutive patients with strokes. 13 were associated with evidence of occlusive disease of the internal carotid artery. More peripheral lesions were often found, and so were clots in the carotid artery itself at operation. This was regarded as evidence of a possible embolic cause for the strokes. Allowing for those cases in which the occlusion was complete, and some operative failures in the cases where the vessel was patent but stenosed, the Memphis workers considered that somewhat less than 5% of patients with strokes could be benefited by a carotid reconstruction operation.

Even less certain, but even more exciting, are the prospects of a similar operation for angina pectoris. In a film Dr. WILLIAM LONGMIRE, Jr. (Los Angeles, Cal.), showed operations for thromboendarterectomy of the coronary arteries in 11 patients with very severe angina pectoris. It was possible to detect the block by simple palpation; and after testing the effect of acute occlusion of the distal, patent part of the coronary artery concerned, fairly extensive removal of the tubular atheromatous plaque was undertaken, using Cannon's small ring strippers, and suture repair of the incision was completed. 6 patients died, 4 during the operation. Of the 5 others, good relief was obtained in 3, lasting in 1 case, up to date, fourteen months. Selection was difficult, but operation at present should be reserved for patients who had angina at rest, and whose exercise pain was accompanied by a depression in the ST segment, resolving towards normal on resting. Preoperative coronary angiography might help in finding the small localised and early lesion.

On a much bigger scale, and equally formidable, was the work described by Dr. GEORGE C. MORRIS, Jr. (Houston, Texas), in a commentary on a film produced in collaboration with Dr. M. E. DEBAKEY. Here an aneurysm of the aortic arch had been resected, using a temporary shunt in the form of a 'Dacron' bypass graft, and finally achieving, by staged connections of further grafts, a replica of the normal aortic arch with its three great vessels, in dacron cloth tubes. The patient was shown ready to leave hospital on the fourteenth day after operation.

In another film Dr. E. S. CRAWFORD (Houston) showed how reconstructive methods can be applied to localised obstructing lesions of the main bronchi. 5 patients had been relieved of the handicaps of total pulmonary collapse, yet had retained their lung, after resection and end-to-end anastomosis of the lesion, which was an obstructing hæmatoma in 1 case, an inflammatory stricture in another, and traumatic rupture and stenosis in 3. In 1 of the traumatic cases the patient had been disabled for eleven years.

What's New in Surgery

Under this heading members of a team each gave a quick résumé of developments in his own subject.

Neurosurgery

Dr. RICHARD SWEET (Boston, Mass.) cited the favourable reports from Chicago on the implantation of radioactive yttrium into the pituitary in the treatment of cancer deposits from the breast: no deaths, and none of the usual complications from the puncture which troubled most earlier workers. From Freiberg had come the results of similar implants for anterior-pituitary adenomas in a hundred cases followed for five years. In London, Ontario, and in Heidelberg the remaining bed after excision of gliomas had been irradiated with isotope applicators, with prolongation of life. In Berkeley, California, alpha particles with the energy provided by 900,000 m.e.v. had been used to destroy the pituitary and other deep tissues by focusing the last, destructive, few millimetres of their path on the point which required the treatment. In Uppsala a less powerful source had been tried in the treatment of parkinsonism.

Abdominal Surgery

Dr. CLARENCE DENNIS (New York) noted the interest now being taken in the transplantation of whole organs by the use of vascular anastomosis—e.g., liver (Boston) and the whole small bowel (Minneapolis). Similarly the study of isolated perfusion of organs—notably the liver (Boston and Buffalo)—was proceeding well.

As regards portal hypertension and parenchymal liver failure Dr. Dennis cited work on deamination, by the use of injected formaldehyde, in preventing meat intoxication in dogs with an Eck fistula. The ammonia-tolerance test, since it depended on the presence of shunts, might be used to give information about them, but not if liver failure was severe. The portal venous pressure could be reduced by posterior-pituitary injection in dogs with end-to-side portal systemic shunts: measurements of the pressure along with the degree of oxygen saturation showed that they both fell together with posterior-pituitary injection, so the action of this agent might be to close arteriovenous shunts in the stomach and bowel.

New work on the pancreas included arteriography, measurement of antibiotic and enzyme blood-levels, and the detection of pancreas specific antibodies, sometimes after the injection of pancreatic tissue; one patient had been found to have auto-antibodies to his own pancreas. Thus there was a prospect of further use of precipitin tests in pancreatic disease. β-glucuronidase and leucine amino-pepsidase were being estimated in pancreatic disease.

Hidden gallstones might be detected by the use of ^{131}I-treated rose-bengal dye, which could be layered on to the stones by injection before operation, and special probe counters were used to explore for them at the subsequent operation.

In the prevention of peptic œsophagitis a dialysable extract of the gastric juice had been found effective in dogs: its repeated injected had led to achlorhydria, and later to atrophic gastritis. Other factors controlling acid peptic digestion were the normal pancreas and its drainage (exclusion procedures caused an increase, so the anastomosis should be near the ampulla of Vater, or into the stomach), and, as far as duodenal ulcer was concerned, the mode of emptying of the stomach. A jet had been found to cause ulcer, while a steady stream did not. If the antrum was to remain after gastric surgery for ulcer, it must be denervated, in the acid stream, and not be subject to stasis. Dumping syndrome had received further study. In the Billroth-I preparation the objective accompaniments of the syndrome could be prevented by removing the pyloric mucosa and joining the upper gastric mucosa into the lower sleeve. Water shifts in the syndrome were not large enough to account for the hæmodynamic phenomena. Intrajejunal instillation of sugar solution in volunteers had been found to produce a measurable amount of 5-hydroxytryptamine in the urine, but none had been detected so far in " dumpers ". Dr. Dennis attached much importance to the recent work on closed, circular, ileocolic loops into which the bile was also admitted. Death in jaundice occurred in four or five days in these preparations, but the administration of antibiotics had kept such animals in good health for as long as five months.

Plastic Surgery

Dr. BRADFORD CANNON (Boston, Mass.) said that in homotransplantation by the millipore-chamber method, Boston workers had so far found only limited functioning survival. The least successful tissues for this type of homografting were those with a high oxygen consumption, such as liver or adrenal.

Neoplasms

Dr. WILLIAM J. GROVE (Chicago) remarked that protein metabolism and tumour metastasis were directly related. Cold stress also led to more tumour " takes ". Nitrogen mustard on the other hand appeared to exert no adverse effect on host resistance. Cell-free filtrates of fresh human tumours had been used to induce malignant neoplasms in newborn and some adult mice and hamsters. The tumours thus produced bore no resemblance to the human ones from which they were thought to have been derived. Adenocarcinoma of the human breast was a particularly potent source, especially if the recipient animals were pregnant. This effect was reversible and repeatable with parturition and further pregnancy.

Fat-embolism

Dr. CRAWFORD J. CAMPBELL (Albany) recalled work done in Kansas on fat-embolism. In the first few days lipuria was present, representing perhaps a hidden mechanical block with fat. At five to eight days, however, the serum-lipase was elevated.

Cardiovascular Surgery

Dr. OSCAR CREECH, Jr. (New Orleans), said that in cardiac bypass metabolic acidosis was a serious danger which could be averted by adequate oxygenation. Where after bypass the cardiac output was low and the venous oxygen saturation was low, mortality was high. Combined methods using hypothermia might be useful in this respect. Low flow-rates could also be used, and hypothermic cardioplegia seemed to be a safe method now. Quinidine appeared to reduce the incidence of arrythmias in deep hypothermia. Deep hypothermia could protect the subject against up to 900r total-body radiation. Irradiation itself had been used experimentally to increase the tolerance of dogs to ligation of their anterior interventricular coronary artery; up to 75% survived, compared with the normal 11%. In British Columbia work was in progress on a selective supravital stain for the cardiac conducting tissue, helping to avoid damage to it during open heart operations for ventricular septal defect.

Open Heart Surgery

Dr. DWIGHT C. MCGOON (Mayo Clinic) declared that auricular septal defects could and should be closed in almost every case, with a risk of 1–2% where there was no history of heart-failure, no pulmonary hypertension or increase in the pulmonary vascular resistance above half the systemic value, and no rise in right auricular pressure. The presence of two or more of these factors entailed a much higher operative mortality. Dr. McGoon believed that in future all such cases would be treated by cardiopulmonary bypass. At present at the Mayo Clinic the " well " or semiopen method of Gross was preferred. Some ventricular septal defects were easily repaired. Ostium primum lesions with a cleft mitral leaflet were comparable with auricular septal defects. Closure was attended by a 4–5% mortality, and though heart-block occurred in half the cases it was not so severe as after ventricular septal defect (V.S.D.). A small V.S.D. beneath the leaflet might safely be left open, particularly as deep sutures might injure the bundle. With the more severe type of V.S.D. both lesions required repair; the present mortality of over 60% was discouraging, but the untreated cases did so badly that operation was still indicated. Small shunts with no pulmonary hypertension were left alone at present, the main risk being infective endocarditis. If pulmonary vascular resistance was high no benefit could be expected from operation. The intermediate types should be treated surgically. Ischæmic arrest for fifteen to twenty minutes allowed ample times for suturing. Bundle block was lessening with greater experience, but 10–20% of patients had residual defects following closure. For the tetrad of Fallot the Mayo Clinic practice in the past three years had been to use the open method of repair whenever possible. If unsuitable for this, patients could be given an indirect operation with the prospect of a curative procedure later. Median sternotomy was the best approach for their type of operation. Widening of the outflow tract with a prosthetic patch was used in two-thirds; but it was important not to overdo this, for a virtual cardiac aneurysm might result, and lead to further cardiac impairment. Mortality in this group (20%) was higher than in most congenital heart operations, but 60% of the remainder had virtually perfect results.

Dr. C. W. LILLEHEI (Minneapolis) set out the essentials for success in cardiac surgery. Perfection must be sought in diagnosis, perfusion practice, surgical technique, and immediate postoperative care. For example, the patent ductus patient with pulmonary hypertension might also have a septal defect, or the V.S.D. patient a coronary arterioventricular fistula. In acquired heart-disease a left ventriculotomy was now considered a prerequisite to efficient correction of the valvular disease. The amount of aortic disease could be assessed, and deliberate attempts to improve it were better than the blind splitting which had been used in the past. For elective cardiac arrest they had been using selective cardiac hypothermia for nearly a year, and with a special pump adaptation could reduce the heart temperature to 20°C in three to four minutes. Elegant open techniques for the cure of mitral

insufficiency were shown, including one attractive prosthesis with a silastic valve mounted upon an ' Ivalon ' cushion, thus correcting annular and valvular insufficiencies at the same time. One patient had been given a similar silastic prosthesis to replace his aortic valve, and had survived a year after the operation.

LEARNING AND TEACHING

FOR the second annual conference of the Association for the Study of Medical Education (ASME), held in London on Oct. 15 and 16, the theme was Methods of Learning and Techniques of Teaching. In an opening address, Sir ROBERT PLATT said that ASME was anxious to know more of what medical schools were doing in the way of curricular and other reforms. ASME now had wide contacts, extending over many countries, and Sir Robert spoke appreciatively of the part played by its secretary, Dr. John Ellis, in broadening the range of ASME's influence.

Incentives to Learning

Dr. W. D. WALL, director of the National Foundation for Educational Research, brought an infectious enthusiasm and provocative incisiveness to his discussion of this topic; and a comment on the traditional British approach might lie in the error of at least one of his audience in believing him to be an American. He distinguished between motivation (the psychologist's word for some pressure from within the organism) and incentive (the external stimulus). Teachers often tended to neglect motivation and to drive or coax rather than " develop " their students. In the external stimulus, some anxiety-provoking features seemed beneficial to learning, and there was probably an ideal level of anxiety: too much clearly impaired performance, and the completely " never-a-care-in-the-world " outlook might mean that the student was operating below his best level. The social climate of groups of students had much influence on learning ability. To secure the most beneficial cooperativeness in a group, the democratic system was best, in which the teacher was primus inter pares, guiding only when necessary. The inert laissez-faire teaching organisation (which unhappily could be mistaken for the truly active democratic order) led to disintegration; and authoritarian methods generated hostility. In an experiment at the Massachusetts Institute of Technology, two matched groups of students were put in situations where the stimulus of competition could be compared with the benefits of cooperation. In the competititive group, barriers sprang up between students and teacher; and in the cooperative group productivity, friendliness, and (strikingly) pressure towards achievement were notably greater. Dr. Wall put a series of telling questions to the conference, some of them particularly searching for medical teachers. How far did we impose methods of learning because we suffered them ourselves—a sort of relentless sadism? How long must we adhere to the nonsensical view that the acquisition of a mass of facts strengthened " mental fibres " and was a healthful form of mental discipline? Did we need to lecture in order to teach effectively?

Rats and Mazes

Psychologists, observed Prof. G. P. MEREDITH, professor of psychology at Leeds, had 29 theories of learning, most of them derived from a study of rats in mazes. The hope was to work up the scale from rats, reaching the medical student perhaps in 3000 A.D. One difficulty was that rats did not talk and students did, often saying what their teachers did not relish. All too often, the present assumption was that if teachers did their best and students failed, then the students were lacking in ability or health. Students' comments were very largely concentrated on their living conditions and on financial pressures, on the framework in which the teaching process went on, rather than on the process itself. Professor Meredith wanted documentation and teaching needs to be more closely related, and research into documentation could be a useful guide to better ways of helping the student through the maze. A study of library classification, for instance, could itself be an active educational factor in promoting an analysis of relationships. But enthusiasm for information technology and the benefits of " automated retrieval " of data should not be allowed to obscure the fact that the maze was not automatically made more acceptable to the student by mechanising and electrifying it. If the rate of learning was to match the acceleration of research, some new factors in learning processes must be exploited.

Teaching Anatomy

Dr. T. A. QUILLIAM described methods now used in the anatomy department of University College London. The present course was a compromise between the Continental system, with its insistence on great morphological detail, and the American method, which aimed at a much more general picture. The time devoted to lectures had been cut by a half; and Prof. J. Z. Young began the course with a group of lectures introducing the student to the study of man. Progress was supervised four or five times a term when a teacher acted as chairman of a small discussion group of students who had been studying a particular part of the body. The collection of data (and illustrations of the hazards of biological measurement), clinical demonstrations by surgeons, and unconventional elective classes were other features of the course.

Prof. G. A. G. MITCHELL (Manchester) wondered whether the emphasis on departmental teaching was the right one. Were departments of anatomy and physiology outmoded? Was it still necessary to dissect the whole body?

The Harvard Reform

At the University of Harvard a special year's course in basic medical sciences was established in 1952, open to undergraduates working for both M.D. and PH.D. degrees. It was so successful that 3 years ago the preclinical course for medical students was remodelled on similar lines. There was no rigid laboratory schedule: time was not allowed to be a deterrent, and the schedule was shaped to fit the experiment, not the reverse. As Prof. E. G. BALL, chairman of the division of medical sciences, illustrated, work was now based on organs and organ systems, as compared with the former arrangement under which, for instance, the kidney and its function were studied at six widely spaced periods during the two semesters. A " home laboratory " was provided, to which students had a key and could come and go at any time. One teacher was assigned to the course from each of the departments of anatomy, bacteriology, biological chemistry, physiology, pharmacology, and pathology; and in the 7 years since the course began each department has had three and some four members on the course. The growth of enthusiasm among teachers as they tasted the flavour of the new approach had been remarkable. The students' interest had been caught too; the library was much busier and many more wanted to work in the summer vacation. Challenged to say whether this kind of course provided the basic content of factual knowledge that many people thought necessary, Professor Ball said he thought it was more important to teach students the facility to use knowledge and where to find it than to instil it in bulk.

Original Work

Discussing the value of original work, Dr. P. J. RANDLE, lecturer in biochemistry at Cambridge University, held that people could not be taught to be original but they could be given the opportunity to display originality. Research problems were enormously popular with students; and in pursuing them, it often turned out that techniques, which had perhaps presented some difficulty in the ordinary class, assumed their correct proportion when they became part of some wider interest.

Principles of Learning

Students could benefit from being made conscious early in their career of principles of learning that had been helpful to others; and at Edinburgh University, Prof. ALEXANDER KENNEDY said, first-year students were told about methods of study. And this year students were to study the learning pro-

cess in themselves, as an introduction to applied psychology. Learning was not just remembering: a "world image" was needed to arrange the facts, and the framework on which to hang them was built up from childhood. Some rules had been established for efficient memorising: the task should be tackled when the learner was fresh and he must work at high intensity; imprinting must be full and accurate; large chunks of material should be absorbed at a time; and the subject should be revised fairly soon after learning and occasionally thereafter. But students tended to become preoccupied with memory, and they should realise that it was no good filling the mind with unimportant facts. Probably more important than anything else to successful learning was interest. The phasing of study was significant, and frequent class examinations might place the memorising peaks too close together.

Learning from Patients

From patients, we could learn facts and we could learn about people, Prof. M. L. ROSENHEIM declared. The outpatient department was the place where students (in very small groups) could see how a doctor handles patients and their problems; and the emphasis here should be on patients as people rather than on the facts of their illnesses. In the wards a critical research atmosphere was a valuable stimulus to interest and enthusiasm in the student. Registrars and house-physicians should discuss students' notes in detail with them, and the students should know that their notes were appreciated by the physician. Referring to the preregistration year, Professor Rosenheim said that some students had considerable difficulty in coping with the responsibilities that it involved and might need psychiatric help. It was the fault of clinical teaching that such troubles did not come to light until the preregistration year. It was high time our universities did what they could to improve training in the preregistration year by encouraging higher standards in hospitals offering preregistration posts.

Aids to Teaching

Prof. J. K. RUSSELL (Newcastle upon Tyne) had been exploring the possibilities of a clinical teaching room [1] adjacent to the ward, and he illustrated how it had been used to enliven teaching in obstetrics and gynæcology, notably by the display of coloured transparencies. In another experiment, he had recorded his history-taking interviews with patients, and he played to the conference a tape depicting a typical history of placenta prævia, which could be compared, for example, with a history recorded by a patient who had had an accidental hæmorrhage. Not everyone was enthusiastic about this device, and Prof. G. R. HARGREAVES (Leeds) detected too much hindsight in the specimen recording. He thought that a better way would be to record *all* interviews and scrap the nine-tenths that were no good for teaching purposes.

Dr. R. C. MAC KEITH thought that visual aids were valuable in medical teaching but they must be well produced and skilfully used. Too often the lecturer's familiarity with his subject beguiled him into showing incomprehensible slides or displaying visual material for too short a time. Films could be very effective and their teaching value had been amply demonstrated. Dr. Mac Keith showed short films of the movements of the small intestine, the intestinal villi, and the draught reflex, which confirmed his claims. He wanted to see more interchange of good teaching visual aids in order to spread costs and reduce duplication of effort. His plea for perfection was reinforced by Miss SYLVIA TREADGOLD, and that incited Professor KENNEDY to put forword the claims of the slightly imperfect to be a stimulus to indirect learning because it encouraged the student to make his own syntheses.

The Tutorial System

Dr. JOHN BADENOCH described the evolution of the tutorial system for clinical students at Oxford. Earlier experience showed that a series of tutors and too frequent meetings of tutor and student could decline into coaching sessions. To avoid this and other difficulties, the clinical student now retained a single tutor throughout his clinical years. This tutor was a senior member of the university staff or a consultant. The purely professional aspects of the tutorial system were undertaken as weekly seminars in the wards, conducted by the more junior teachers. The discussion made it clear that many medical schools were organising tutorial systems which had to be tailored to fit the traditions and needs of the individual schools.

1. *Lancet*, 1958, ii, 444.

Evaluation of Techniques

Prof. MILES WEATHERALL, professor of pharmacology at the London Hospital Medical College, discussed the methodology of evaluating experiments in teaching. Uncontrolled experiments were valueless, failing to provide valid evidence and fostering opinions based on conjecture or prejudice. Unfortunately means for measuring the effectiveness of teaching were either expensive or unavailable. He referred to a controlled experiment designed to test whether factual knowledge was gained more efficiently by lectures or reading. The results showed that lectures were more successful in achieving this limited objective, and that some lectures were more successful than others. Such experiments were only a beginning and so far no techniques had yet been worked out for the objective controlled evaluation of the other more important skills which medical education was intended to impart.

RADIATION INJURY AND MARROW TRANSFUSION

FROM A CORRESPONDENT

A CONFERENCE on clinical aspects of radiation injury and transplantation of bone-marrow and other organs, held at the National Institutes of Health, Bethesda, Maryland, on Sept. 18 and 19, was one of a series relating to radiation injury, and its main interest, for clinicians and hæmatologists, lay in the presentation and discussion of most of the work done so far in the treatment of leukæmia by irradiation and marrow transfusion.

Chemical Protection

It has been known for some years that sulphydryl (–SH) groups protect animals and humans from the toxic effects of nitrogen mustards, but, recently, compounds such as aminoethyl isothiourea (A.E.T.) have been found to protect mice against the lethal effects of irradiation as well as against alkylating agents. The chemistry and properties of A.E.T. were described by Dr. D. G. DOHERTY (Oak Ridge). The mechanism by which its protective action was mediated remained obscure. Dr. M. KELLY (National Cancer Institute) gave evidence that the LD_{50} of A.E.T. was much lower in dogs than in mice and there was little significant protection in dogs. Dr. J. V. SCHLOSSER (Tulane) found that A.E.T. produced a number of side-effects in man, including rashes, hypotension, nausea, vomiting, cramps, and hæmolytic anæmia, whether given by mouth or intravenously, and there was as yet no convincing evidence that it had significant protective action in man.

The best protectors against alkylating agents seemed to be the mercaptans and cystein, but, as Dr. PETER ALEXANDER (London) pointed out, total –SH groups exerted far more effect in protecting against nitrogen mustards than against irradiation; there was no evidence that the mechanisms involved were the same or even related.

Other protective agents discussed were *p*-aminopropiophenone, which unfortunately produced methæmoglobinæmia, and colchicine and salmonella endotoxin, which were surprisingly effective in protecting the marrow and speeding the onset of marrow recovery after irradiation. Dr. WILLY SMITH (National Cancer Institute), describing these phenomena, postulated that stimulation of stem cells directly by these agents, or of a humoral agent which stimulated the stem cells, were the likeliest explanations for the observed effects.

The impression was that studies of the selective effects of all these agents, and of such factors as the critical time relationships between dosage and effects, might offer ways to further knowledge about tumours and their treatment, but that at present the practical value of these protective agents was slight.

Clinical Data

Dr. G. MATHÉ (Paris) described the illnesses of the 6 Yugoslavians who were accidentally irradiated last year in an accident with a nuclear reactor. It was calculated that they had received between 450 and 1000 rads. The most severely affected was given two transfusions of marrow; the first, of myeloid cells from a 5-month-old child, was ineffective, but a second, of twice as many cells from an adult donor, was partially effective and a similar dose was given to 4 of the others. Using the Ashby red-cell-survival technique it was calculated that the transfused marrow continued to produce red cells for about a month and then gradually died; but it seemed unlikely that marrow transfusions were of benefit in these patients.

Dr. G. A. ANDREWS (Oak Ridge) described a patient who accidentally received about 600 rads, showed severe depression of the red and white cells of the blood 4 to 6 weeks later, and then had a rapid response without transfusions. He received antibiotics only for specific infections. His blood now showed persistently low normal white counts and platelets. Capt. J. KING (United States Navy) made it clear that in the management of radiation casualties the course adopted by the Navy would follow very much that outlined by Dr. Andrews and that they were prepared to wait at least 1–2 weeks before making a decision about bone-marrow transfusion. A special unit to deal with such casualties is being built at Bethesda.

Dr. MATHÉ described his treatment of 6 children with leukæmia. Remissions were obtained with steroids, and 6-mercapto-purine was then given during the remission. This was stopped 1 week before giving 800–1000 rads. The immediate results were alopecia and skin rashes, a disturbance of serum-potassium which was difficult to correct, and a fall in the prothrombin consumption, followed by depression of red and white cells and platelets. Each child received 10 billion nucleated cells from its mother's marrow, in a volume of 270–650 ml. between 3 and 14 days after irradiation. 2 children died with complete aplasia and no evidence of regeneration. There was temporary recovery in 4, 2 of whom went into remissions lasting 6 months. In 2 there was good response to marrow transfusion initially; but after 2 weeks the lymphocyte-counts fell, the patients developed diarrhœa and fever, and then underwent some recovery in their general condition as the donor marrow disappeared. Dermatitis and hyperkeratosis developed, and their condition was not unlike that seen in animals with " secondary disease ".

Dr. ANDREWS treated 11 patients with leukæmia in partial remission on steroids and antimetabolites (the latter were stopped before irradiation). Doses of 200–900 rads were given. Marrow transfusions followed within 4 days. In 2 patients there appeared to be exacerbation of leukæmia with rapid proliferation and death. 3 showed sustained partial remissions, 3 had " complete " suppression of the leukæmic marrow and went into prolonged remissions, 3 showed suppression but died in an aplastic phase, and 3 showed suppression but died soon after irradiation. A most interesting observation was that bone-marrow recovery after X-radiation seemed to occur about 2 weeks sooner in the leukæmic patient than in accidentally irradiated normal subjects receiving approximately equivalent doses.

Dr. DONNELL THOMAS (Cooperstown) had found fœtal marrow transfusion useless and adult marrow effective in a child who received 900r; and Dr. N. B. KURNICK (Long Beach, California) described work now in hand to use homologous marrow by taking marrow from patients with leukæmia in induced remissions, storing it, and then transfusing it back into the same patient after irradiation. In this way better " takes ", with the avoidance of postulated " secondary disease ", might be achieved.

Irradiation and Infection

The final session was concerned with ways in which infection of irradiated subjects might be minimised. There was some evidence that animals such as chicks and mice survive irradiation better if they have been reared under germ-free conditions. Such a situation could never be reproduced in humans, and the general opinion was that the usual methods of minimising infection, so seldom properly applied, were the only ones capable of practical application.

The general tone of the meeting was not optimistic, but it was clear that the present lines of attack on leukæmia have not yet been fully prosecuted and later results may be more encouraging.

Medicine and the Law

Treatment Refused

A WIFE applied to a magistrates' court for a maintenance order against her husband on the ground that he had wilfully neglected to maintain her. The husband contended that she was not entitled to be maintained by him because she refused to live with him unless he agreed to undergo E.C.T. treatment which had been prescribed for him; he further contended that he was prevented by illness from working.

In December, 1955, the husband, a miner, injured a knee at work. Thereafter, he became convinced that the condition of his knee disabled him from working regularly, though repeated medical examination and X rays disclosed no abnormality, and he had been repeatedly assured by doctors that there was nothing wrong with his knee. Later, he developed the further belief that he had a broken back and could not be reassured that in fact no such condition was present. He often took days off work, lying in bed or sitting at home. He spent several short periods as a voluntary patient in a mental hospital; on the last occasion he discharged himself, having refused E.C.T. as advised by the hospital. The wife thereupon refused to live with him again unless he agreed to the treatment.

The magistrates made a maintenance order and the husband appealed to the Divisional Court. The Divisional Court dismissed the appeal. Lord MERRIMAN said that it appeared that the reason the husband had refused the E.C.T. treatment was that he was satisfied that there was nothing wrong with his head and that shock treatment would not do any good to his back. The magistrates were entitled to take the view which they had taken that the wife was, in the circumstances, entitled to insist on the husband's undergoing the prescribed treatment as a condition of her resuming cohabitation with him.

If a husband, by some form of disablement, were prevented from earning a living, that would obviously be relevant to the question whether a failure to maintain his wife was due to wilful neglect. If, however, the evidence showed that a simple operation might cure the disablement, the position might be different. That would apply to mental, as well as physical, disability. It had been argued on this husband's behalf that his refusal to undergo E.C.T. was due to a delusion that it was designed to cure his back. Such a delusion, if proved, could have the same legal effect as an uncured physical disability. Proof of such a delusion would have required medical evidence and, in particular, evidence from the mental hospital where the husband had been a patient. No medical evidence had been called. The magistrates were justified in holding that the husband was capable of working.

Stirland *v.* Stirland. *Divisional Court:* Lord Merriman and Phillimore *J.* Oct. 12, 1959. Counsel and solicitors: Charles McCullough (Sidney C. Elphick for Claytons, Nottingham); R. D. Lymbery (Church, Adams, Tatham & Co. for Healey & Smith, Nottingham).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

AFTER attending a conference on medical education, I am looking forward to the brave new world which is on our doorstep. With such a galaxy of distinguished professors and consultants inspired by a common purpose it can be only a few years before we have, everywhere, an integrated course in medicine. Structure and function will be correlated, the clinical lion will lie down with the preclinical lamb (the lamb may be inside the lion by then, but that will only integrate the process of lying down), and the students will be taught everything by everyone simultaneously and continuously for five years, thus ensuring vertical as well as horizontal coordination and much more free time for students.

I am looking forward to this time particularly because I shall then be able to put forward a revolutionary system of medical education. It will be called progression, because progress is always O.K. and the course will consist of going on one step at a time. Students will first learn reading, writing, and arithmetic, then some physics, chemistry, and biology, later anatomy and physiology, and so on. Each department will provide courses at its own discretion, and its teachers will be free to teach for twice as long because they will no longer be spending time on committees to arrange integration. Students will meet every aspect and organ of the body on numerous separate occasions, and there is abundant evidence that it is the repetition which makes knowledge stick. Students will be shown problems from different angles and will have to think for themselves (with their teacher's advice if they ask for it): when they have done this they will be somewhat wiser. They will be spared the total lack of stimulus provided by the perfectly predigested, smoothly integrated course. Courses will sometimes clash, and students will show which course, if either, they find most useful because they will make up their own minds which to attend.

This progressive course will be highly original and wildly attractive as a substitute for the by then universal integrated system. Its very novelty will assure its success, and I hope I shall get the job at Eastern Perverse where it will be initially introduced. I shall save a lot of time by taking any old set of M.B. regulations for the exams and courses, and I shall get on with undisturbed teaching as usual, thus showing the dramatic success of the new concept of progression.

And there will still be not a shred of scientific evidence from a single controlled experiment to prove me wrong.

* * *

My week in camp as an assistant scoutmaster was a success. A few first-aid things thrown into a haversack gave me the pretence of being the doc, and one stubbed toe, one toothache, and one minor abrasion did not overtax my capabilities. My real duties were to keep the camp bank and take my turn with the duty patrol. As usual with amateur accountants, the bank didn't quite balance and I showed a small loss. In contrast my cooking activities usually showed a surplus at the end of each meal.

Perhaps my hardest task of all was to take a party of scouts to the sea and then sit wondering who would drown and who would kill themselves rock-climbing. Statistics I was given indicated that in our district rock-climbing was the greater danger. I am glad to say we did not modify the statistics, but I was left full of admiration for those who year after year take scout parties to camp and give the boys a chance to try out their potential on something less antisocial than flick-knives and bicycle chains.

* * *

Ours is a North-country hospital, and the usual Hallowe'en party ended with ghost-stories in the residents' common-room. Macabre, the pathologist, had a complicated tale about a chef who cut his throat in the kitchen after drinking meths., and no matter what vegetable his successor tried to prepare, it always came out red cabbage, while the chef's ghost cackled hideously behind the refrigerator. "That's the worst of these methylated spirits," said Ananias, and had we heard about the House of MacGrolloch's Harbingers of Doom, who were two large bowler-hatted men with big boots, and whichever member of the clan they confronted disappeared for anything up to ten years.

"Uncanny, you will say," continued Ananias, beating Macabre to the gin-bottle by a short hand, "yet commonplace beside the manifestations which occurred when Theo. Grayte-Reaper, alias the Abominable Showman, was operating upon Madame Stella, the virtuoso of the ouija-board and professional medium. Grayte-Reaper being partial to a gastrectomy, we were having a stab at that, plus removal of appendix, the sentences to run concurrently, and Grayte-Reaper was happily laying about him with his flensing-knife when Madame's control, an immense Red Indian called Big Chief Flying Saucer or some such utensil, materialised alongside the surgeon and handed him a tomahawk instead of the artery-forceps.

"Flying Saucer apparently expected, with some justification, that Madame Stella would be joining him on the Other Side at any moment, and said that ever since he had signed her on his list she'd done nothing but call him up night and day on the ouija-board, but what else could you expect on the Supernatural Health Scheme and if she actually did Pass Beyond his after-life wouldn't be worth living. The Happy Hunting Grounds would, he felt, be distinctly less Happy with Madame doing the hunting.

"The whole uncanny situation was aggravated by Flying Saucer addressing Sister as Pale-face Squaw, saying what a nice wigwam she was wearing, and then setting fire to Grayte-Reaper's gown with the diathermy-cautery in order to send a smoke-signal. Also the seventeen extra swabs we finished up with turned out to be ectoplasm and it took us three-quarters of an hour to get it all back—I'd sooner try and put the froth back into a bottle of beer . . ."

"I'll bet you would," said Macabre, "but you've already drunk 50% more beer tonight than anyone else. Anyway, why didn't you write up this improbable operation for *The Lancet*?" "We would have," said Ananias, "but Grayte-Reaper felt the G.M.C. might disapprove of his unqualified assistant."

* * *

The coroner didn't like me. But in the days when it was the resident's sole source of income a visit to the coroner's court was no occasion for gloom, and perhaps my demeanour as I entered the witness box was not as subdued as it might have been. At any rate he looked me over so hostilely that my mantle of omniscience suddenly felt threadbare and I was almost rattled as I began to take the oath.

"I swear by God Almighty . . ." I began.

"You may be in the habit of so doing," an icy voice intervened, "or you may think it scans better that way round. But in this Court we prefer a slightly different arrangement. Now begin again, and this time read from the card."

* * *

Whenever I watch sheep-shearing my thoughts turn to the analogous process now largely performed by the electric shaver on the human animal. Of course we are at a disadvantage since we have to submit to this procedure 364 times oftener than a sheep. Mind you, I was brought up in a sterner tradition and a different technique, which can be regarded, I think, more as a surgical skill than a mere farming routine. I refer, of course, to the soi-disant safety razor with which I have regularly, but fortuitously, obtained Reverdin and at times even something approaching Thiersch grafts.

But, there is another aspect of the matter: I reckon that I have had 16,425± shaves to date, occupying about 166 man-hours. Allowing for blades, soap, and depreciation and replacement of plant (blade-holder), each shave has cost at least 1*d.*, which works out at about £68 so far. If I could stand up to domestic disapproval, I'd have grown a beard long ago.

* * *

Thoughts in a Five-star Hotel

Why travel so far
To drink in a bar?

Letters to the Editor

THE COCKETT/ELGAN JONES (ST. THOMAS'S) OPERATION

SIR,—The Cockett/Elgan Jones operation referred to by Dr. Rivlin (Oct. 3) as the St. Thomas's operation emerged from the sweat, toil, and inspiration of these men. It gave us the anatomy, relations, and physiopathology of the ankle perforating veins, and showed us how they became incompetent and caused eczema and ulceration. For fifty years surgeons had ligated large veins at the ankle (I started doing it in 1941), but we didn't know where, how many veins there were, and how they came to be incompetent. I consider that this procedure is as notable a milestone in the treatment of the venous disorders of the lower limb as was the Brodie-Trendelenburg ligature of the long saphenous vein.

The diagnosis in my series is 30% varicose, 30% ankle perforating veins, and 30% both (the remainder are rarities).

I have done upwards of 500 ligations of ankle communicating veins, and have found it a first-class procedure for all ages. The oldest done was 80, and she is still circulating at 86. An encouraging follow-up was published [1] in this journal in December, 1957.

I think it is an operation to be done only after a diagnosis has been made, based on symptoms and physical signs. It is not a procedure for the occasional surgeon. As with all radical surgery, points of management ensure its success. It has restored all my patients to circulation appropriate to their age-group. Recurrent ulceration occasionally occurs, mainly after trauma, but the benefits and activity by far exceed the results from bandaging only. The only physiotherapy those under my care have received (I see 60 to 75 per week) is that of following their daily occupation. They wear protection appropriate to their healed limbs. The scar, after 20 to 30 years of ulceration, cannot safely be left unbuffered.

I have found the ligation of ankle perforating veins a major contribution to the cure of much recalcitrant ulceration in all social classes.

London, W.1. HAROLD DODD.

TOLBUTAMIDE CONTROL OF DIABETES MELLITUS

SIR,—Some aspects of the interesting paper by Dr. Joplin, Professor Fraser, and Dr. Vallance-Owen (Oct. 17) merit greater emphasis. It is noteworthy that in 11 of 38 patients receiving insulin but considered suitable for trial with tolbutamide it was found that insulin was unnecessary. This illustrates the undoubted fact that many diabetics are taking insulin needlessly, adequate dietary control being all that is required. But there is evidence that many patients now receiving sulphonylureas continue this therapy quite unnecessarily. It is perhaps due to the careful selection of patients by the authors that this was found to be true in only 1 of their cases who responded satisfactorily to tolbutamide. Nevertheless even this patient might have been continued indefinitely on the drug had trial with an inert tablet not been a regular feature of this investigation. It is noted that this particular patient lost a stone in weight. Is it to be assumed that this was one of the cases referred to as having previously " proved hopeless " in the attempts to achieve " necessary weight reduction "? Since correction of obesity is in itself so essential, and since this alone may be expected to effect satisfactory diabetic control, it is at least debatable whether in such cases the administration of hypoglycæmic drugs is justifiable. It would be interesting to know how the other patients of this type responded in this trial—both as regards weight and diabetic control.

During the period of observation after transfer from tolbutamide to the placebo the authors estimate the state of diabetic control during the second week. This is essential since complete remission may persist for several days after stopping tolbutamide—and for much longer if the drug used has been carbutamide or chlorpropamide—and long after any trace of it can be detected in the blood.

The standard dose of tolbutaminde, 0·5 g. four times a day, seems rather high. We have found the maximal doses for estimating reponsiveness to be, for tolbutamide, 500 mg. thrice daily, for chlorpropamide, 500 mg. once daily, and for metahexamide 300 mg. Increase beyond these doses has rarely if ever improved control, while large doses are probably responsible for many of the reports of toxicity, and therefore not advisable. Did the authors in fact find any benefit when they gave 4 g. daily?

While welcoming the advice to determine whether or not the patient requires either insulin or tolbutamide, I consider there is some danger in dealing with outpatients by their method of transferring from one to the other. Patients had insulin stopped for 48 hours; 2 became ketotic and required insulin immediately. I have seen a similar case lapse within this space of time into precoma and require intravenous therapy. The procedure which we recommend is to reduce the insulin, and then give tablets (we prefer chlorpropamide which necessitates only a single daily dose). If urine tests show excellent control, insulin is further reduced and, if oral therapy is to prove effective, withdrawn. After a period on tablets alone these too are withdrawn, and only if glycosuria and hyperglycæmia recur is it decided that continuing oral therapy is desirable. It is at this stage perhaps that inert tablets might be used—now truly a " placebo " to obviate the fear of relapse which some patients exhibit when it is suggested that they discontinue the tablets in which they have come to place much faith.

The Victoria Infirmary, Glasgow. IAN MURRAY.

THE ÆTIOLOGY OF LEUKÆMIAS

SIR,—In our time we all play many parts. I had cast Dr. Schöyer for the part of the villain who advocates the doctrine of " special evil " of the cancer cell, but I now find from Professor Smithers' letter of Oct. 10 that I am taking that part.

I have for a long time believed that the process of carcinogenesis is an aberration of the maintenance of the normal processes of growth and differentiation in the tissues, as I have stated in print.[1] My work on the relationship of carcinogenesis and regeneration in the liver (in the press), and on the surface properties of cells in tissues undergoing carcinogenesis, and in tumours, is based on such an assumption. It now appears from the last paragraph of Dr. Schöyer's letter that we are at least at one in believing in the importance of the properties of the cell surface, in " the cancer cell " if I may use this latter term. It seems that Professor Smithers attributes much evil to its use.

It is probable that the behaviour of all cells depends to a considerable extent on their environment. No-one who has worked on the liver cell in the " normal " state, in regeneration, during carcinogenesis, and in tissue culture would seriously doubt this. Yet it is convenient to refer to certain general properties of the " liver cell ".

1. Dodd, H., Calo, A. R., Mistry, M., Rushford, A. *Lancet*, 1957, ii, 1249.

1. Laws, J. O. *Med. Pr.* 1958, **240**, 943.

The " cancer cell " varies not only in response to environment, but also in the degree to which its own biological behaviour deviates from the normal. Nevertheless it is a fact of practical importance that one can recognise a tumour by its behaviour, and, as a tumour consists of cells, it would seem that there must be certain " characters " which must be attributed to " tumour cells ".

That the acquisition of all such " characters " is to be attributed to a " single, specific, intracellular heritable change " seems to me to be very improbable. Yet on reading Dr. Schöyer's article I had the impression that this was basically what he was suggesting. I therefore feel that Professor Smithers' support for this hypothesis—that is, the " explanation " of the ætiology of malignancy by injury to genetic material (in other words, induced somatic mutation)—is widely at variance with the general ideas which he puts forward in the body of his letter.

Dr. Schöyer, in his letter, now emphasises the part which may be played by changes in the cell cytoplasm (the surface, for example) in producing the characters of the cancer cell. Surely the emphasis should be on these changes which, whether they are secondary, as he suggests, or primary, as I think, are most likely to be susceptible of analysis, and which may, as I suggested in my first letter, provide us with real clues as to why cancers behave as they do.

Department of Experimental Pathology
and Cancer Research,
School of Medicine, Leeds. JOHN O. LAWS.

A CARDIAC DEFIBRILLATOR: A WARNING

SIR,—I feel that Dr. Lucas should be congratulated for his attempt to introduce for *emergency* use, as he stresses in his letter last week, a piece of apparatus costing shillings rather than hundreds of pounds which may yet save many a life in hospitals whose funds are limited.

Warnings of the shortcomings of such equipment are timely, but with even greater simplification of design the defibrillator would become infinitely safer though never foolproof, and most of the hazards mentioned would no longer apply.

Though the statement will no doubt appear paradoxical, if not heretical, the safest working conditions possible in such an apparatus would, I believe, be obtained by employing an existing wall socket switch as the sole circuit make-and-break with direct and unbroken leads running to the electrodes, whose handles, not least for the good morale of the surgeon, could and should be sheathed in thick rubber tubing. Operation would require the quickest on-off flick of the wall switch by some responsible person, with the advantage that the stimulus could be repeated as simply, as often, and as briefly as desired, and moreover the whole apparatus would be at neutral potential except at the moment of use since the neutral side of the mains socket is never switched.

Time-honoured custom regards fused electrical circuits as synonymous with greater safety, but such fusing should, if used, be in accordance with modern practice in domestic circuits and inserted in the live-side lead only, which would obviate precisely the sort of danger to which Mr. Wyatt (Oct. 17) alludes. A 500 mA fuse rating might come nearer the safety limit he suggests in the event of the switch operator being unable to carry out his duties with sufficient verve. An unlikely event!

If a push switch is considered necessary it should be single pole only. Placing it in circuit on the wall-socket side of the fuse would be more in keeping with sound electrical practice and would avoid any danger of shock to a person changing the fuse, one of whose contacts would always remain live in Dr. Lucas's system.

One final point. The wall socket which it is contemplated would be used in such an emergency should be checked for polarity. Accepted standard practice is that the live-pin socket is the right-hand one facing, and this alone is switched. Incorrect wiring in which the switching has been arranged in the neutral lead has been known, and if undetected would prove remarkably lethal.

Those readers who still feel interested and confident enough to employ this apparatus in emergency would be well advised to construct it themselves or contract to some electrician outside the hospital service ; group engineers are unlikely to cooperate in sanctioning the construction of apparatus not conforming to Ministry standards and for which they would not be " covered ".

I await the holocaust that this exposition will probably bring.

Exeter. P. BUTLER.

RISKS ASSOCIATED WITH MODIFIED ELECTROPLEXY

SIR,—I should like to thank Dr. Crowcroft, Dr. Bates (Oct. 10), and Dr. Davies (Oct. 3) for their comments on my letter of Sept. 19.

Far from being very rare, I suggest that apnœa after E.C.T. modified with suxethonium, &c., occurs much more often than is generally supposed. The terms " apnœa " and " prolonged apnœa " are, I suggest, very loosely used. Apnœa to my mind is strictly defined by virtue of a time factor in that, if respirations have not commenced after three to four minutes, then apnœa can be said to exist. Such factors as weight, age, amount of drug used, &c., must of course be taken into account. Likewise, prolonged apnœa should not be applied until at least fifteen minutes have elapsed.

Some writers emphasise blood-cholinesterase levels as a significant factor yet, as one of your correspondents states, prolonged apnœa occurred in one patient with a normal level. In fact, in the case I reported the blood-cholinesterase was also normal. Dr. Bates comments that there was an impaired myocardium, but I suggest that this was a direct result of treatment and accompanying biochemical changes, particularly a hypopotassæmia; and, therefore, where possible in suspect cases, serum-potassium levels should be estimated before treatment, and potassium chloride given in the event of failure to restore respirations five minutes after giving modified E.C.T.

Warley Hospital,
Brentwood, Essex. F. A. CAMPBELL.

SIR,—Death and near-fatal accidents are not uncommon following electroplexy, but they are rarely reported.[1 2] It is not difficult to explain[3 4] the death reported by Dr. Campbell (Sept. 19). The woman, aged 52, with a " depressive anxiety state " likely had hypertensive heart-disease. From this point of view I would not consider that she was in good physical state for electroplexy. In such a patient premedication should consist of a larger dose of atropine (2 mg.).

The only purpose of administering a muscle relaxant is to prevent fractures during the convulsion. Even though the practice in many centres is to administer a relatively large dose of the succinylcholine-type of drugs, I feel that this is quite unnecessary and adds to cardiovascular depression the aggravating factors of severe respiratory depression and myocardial hypoxia. Except in the vigorous young patient, the physician does not need to exceed 20 mg. suxethonium when as much as 200 mg. of thiopentone is given first.

In patients past middle age it is also wise to give 100% oxygen with intermittent positive pressure by mask, beginning immediately after the administration of the muscle relaxant and continuing until recovery of full spontaneous respiration is obvious.

1. Crowley, P. J. *Lancet*, 1958, i, 376.
2. Dobkin, A. B. *ibid.* p. 640.
3. Dobkin, A. B. *Canad. Anæs. Soc. J.* 1959, **6**, 51.
4. Dobkin, A. B., Olszewski, J. *ibid.* p. 119.

With these simple prophylactic measures, electroplexy can be carried out with much less danger to the elderly and poor-risk patient.

Department of Anæsthesia,
University Hospital,
Saskatoon, Canada. ALLEN B. DOBKIN.

SIR,—I fear I cannot agree with Dr. MacDougall (Oct. 17).

The experience of most psychiatrists over the past seven years amply justifies the continued use of the "modified" technique. This view is particularly held by those of us with long experience of both the "modified", and "unmodified" application of E.C.T. This view is supported by the numbers of patients with recurrent depressive illness, &c., who compare unmodified E.C.T. very unfavourably with the adequate and proper use of an intravenous barbiturate and a short-acting relaxant. If this procedure is well carried out, the anxiety, and even overt fear of the older methods, is removed for these patients.

I used the 'Ectonus' technique for more than two years, and kept strictly to the instructions given, as used by its exponents. Agreed, one can "damp down" the clonic movements very considerably, but surely we are all agreed that most fractures sustained during E.C.T. occur during the initial *tonic* spasm. Fractures do occur with this technique, I can assure Dr. MacDougall, and it has many limitations when compared with the "modified" technique, especially in patients with other physical disabilities, old or recent fractures, or repaired tendons, and those patients over the age of 65, particularly females, with their osteoporotic femurs and wafer-thin acetabuli.

Electroplexy itself is, indeed, a very effective anæsthetic. So, also, is being pole-axed!

Carlton Hayes Hospital,
Narborough, Leicester. MARTIN RAHILL.

THE FIBRE COMPOSITION OF HOSPITAL DUST

SIR,—In his comments on my observation [1] that the fibres in hospital dust are essentially cellulose, Mr. Watson [2] suggests that, due to electrostatic forces, the 'Terylene' collecting screen used in my experiments preferentially attracted cellulose fibres at the expense of wool and other fibres also present in the air. It is unlikely that such forces would be significant in the face of the 325 ft. per minute draught caused by the fan, and moreover Mr. Watson's hypothesis is unsupported by the literature or by direct experiment. Darmois and Marais [3 4] state that 'Dacron' (terylene) acquires a negative and wool a positive charge. Hayek's electrostatic series [5] confirms this, dacron being near the negative end and wool near the positive end. Cotton is approximately in the centre of the series.

Direct experiment in this laboratory with a goldleaf electroscope has shown that terylene fabric is readily charged negatively either by merely opening folded material, by placing open fabric in a 50°C laboratory oven fitted with a forced-draught fan, or by shaking previously dried fabric in the air. The charge obtained by such methods was found to be relatively strong and persistent. Wool was more difficult to charge, but a pre-dried all-wool blanket could be charged positively by opening rapidly or by ironing between sheets of blotting-paper. The charge conferred on the blanket by these methods was weak and it rapidly leaked away. Cotton fabric was charged with difficulty by the rapid opening of dried, folded material. This charge varied in sign and had only transitory existence, leaking away in a few seconds.

Hence, under normal atmospheric conditions, the terylene filter would be negatively charged and both the wool and cotton uncharged. In a very dry atmosphere (for example, in a heated ward in winter) the wool could become positively charged and attracted to the terylene. Thus any electrostatic charges developed would tend to lower the proportion of cellulose fibres collected and not increase it as suggested by Mr. Watson.

Confirmation that the fibres in hospital dust are preponderously cellulose has now been obtained by an entirely different method. Petri dishes containing $2^1/_2$% gelatin (settle plates) were exposed at bed height and the fibres settling on the gelatin layer were recovered by melting the gelatin and filtering it through a sintered glass Gooch crucible. This method collected fibres from a specific site, whereas the forced-draught filter previously used provided an average ward sample. Hence the settle-plate method is more sensitive to position than the other method and it collects more wool if near a bed than if located at a distance. The usual result obtained was similar to that shown previously when using the terylene filter method, over 90% of fibres collected at bed height being cellulose.

C.S.I.R.O. Division of Protein Chemistry,
Parkville, Victoria, Australia. T. A. PRESSLEY.

1. Pressley, T. A. *Lancet*, 1958, ii, 712.
2. *ibid*, 1959, i, 413.
3. Darmois, E., Marais, A. *C.R. Acad. Sci., Paris*, 1953, **236**, 1456.
4. Darmois, E., Marais, A. *J. Phys. Radium*, 1954, **15**, 189.
5. Hayek, M. *Amer. Dyestuff Rep.* 1954, **43**, 368.

PERIODIC MIGRAINOUS NEURALGIA OF WILFRED HARRIS

SIR,—With reference to the article by Dr. Bickerstaff [1] I find it quite justified to call this variety of headache Wilfred Harris neuralgia. He was really the first who described (1926) this type of periodic headache and facial-eye pain. I have two suggestions:

(1) Since the patient's prominent complaint is usually the headache, perhaps it would be useful to keep the original name and call this disease Wilfred Harris' migrainous neuralgia.

(2) In many cases we have found it useful to give daily very small doses of histamine injections (0·1 mg. in aqueous solution intra- or subcutaneously). With 10–20 injections the neuralgia was relieved in many cases. This effect may be a histamine desensitisation.[2] It has proved useful to give a maintenance dose once weekly for a longer time.

Budapest. T. LEHOCZKY.

TREATMENT OF ALCOHOLISM

SIR,—The outpatient clinic for the treatment of alcoholism established by the Church of England Temperance Society at 14, Gloucester Place, W.1, is now to be known as the Reginald Carter Foundation. Patients are seen by appointment and there are no fees. The activities of the clinic are by no means purely medical but also involve the social rehabilitation of the patient and sometimes of the family as well.

The number of patients referred to the clinic has recently increased very considerably and there is, in fact, a depressingly large waiting-list, indicating the need for a voluntary independent organisation of this nature. If, therefore, it is to function effectively it must expand, and the Bishop of London has recently launched an appeal in *The Times* for £50,000 to enable the Foundation to meet its increased responsibilities. Sir Francis Fraser was one of the signatories of the Bishop's appeal.

Earlier this year Dr. M. M. Glatt [3] emphasised that at present there are in existence "hardly any specialised clinics or units for the treatment of alcoholics under the National Health Service and alcoholics are sent haphazardly to the local mental hospital. It has been stressed repeatedly by competent observers that the ordinary mental hospital without a special unit cannot be expected to get the alcoholic's co-operation and to succeed with him". He added that "what seems necessary is the establishment of special clinics and units for alcoholics

1. *Lancet*, 1959, i, 1069.
2. Eszenyi-Halasy, M. *Brit. med. J.* 1949, i, 1121.
3. Glatt, M. M. *Med. Press*, 1959, **241**, 449.

where they feel ' accepted ' by a sympathetic staff experienced in dealing with them, and where they can be treated by a team of workers and a comprehensive (psychological, physical, social, &c.) therapeutic programme ".

This is precisely what the Reginald Carter Foundation endeavours to provide. In such a setting, contrary to what is so commonly supposed, a great deal can be done to help the alcoholic patient.

Reginald Carter Foundation
for Alcoholic Patients,
14, Gloucester Place,
London, W.1.

BASIL M. MERRIMAN
Hon. Medical Director.

HYPOTENSIVE ACTION OF BRETYLIUM TOSYLATE

SIR,—A hypotensive agent of a new type has been described recently by Boura, Copp, and Green. This substance, bretylium tosylate (' Darenthin ') (fig. 1), has

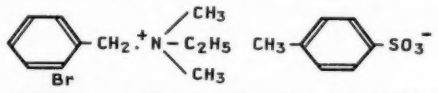

Fig. 1—Bretylium tosylate, N-o-bromobenzyl-N-ethyl:N:N-dimethylammonium p-toluene sulphonate.

been shown by isotope studies to accumulate selectively in sympathetic neurones with adrenergic transmission, and in organs with a predominantly orthosympathetic innervation. The evidence of Boura et al. points towards a blocking action of the drug at such sites, the depressant effect being exerted chiefly at the nerve endings. Of particular interest is the absence in animal experiments of any significant effect upon the parasympathetic nervous system. A degree of toleration has been demonstrated to certain actions of the drug in animals. The clinical use of this compound has been described by Boura et al.[1] who report it to be an active hypotensive agent free from significant parasympathetic side-effects or short-term toxic reactions.

Our own clinical experience with bretylium tosylate, either alone or in combination with other hypotensive substances, covers a series of 218 all-day tests on 33 hypertensive patients. In general our results correspond closely with those of the above authors, minor differences depending no doubt on the method of selection of patients for study. Many of our patients were selected because of the prominence of parasympathetic side-effects with standard ganglion-blocking drugs.

The relationship between the fall in blood-pressure in the lying posture and the fall standing has been compared with the results of all-day tests made previously with various ganglion-blocking drugs: hexamethonium, pentamethonium, pempidine, and 2:2:6:6-tetramethyl-piperidine hydrochloride (M & B 4500), a chemical relative of pempidine which is under clinical trial. There is no clinically important difference among these drugs in the postural effect on the blood-pressure (fig. 2).

The range of dose required to reduce the blood-pressure (standing) to near normal in the trough of the blood-pressure fall has been of the same order as that reported by Boura et al.[1] In the absence of adjuvant drugs occasional patients require as little as 200 mg. daily, others need up to 2800 mg. daily, in order to establish adequate control over the blood-pressure. The average daily dose used in 19 patients who had no other drug was 824 mg. but in 5 of these patients the blood-pressure was not adequately reduced. The maximum single dose used was 1000 mg. The duration of action as with ganglion-blocking drugs depends on the extent of the blood-pressure fall; it has usually exceeded four and sometimes has exceeded fifteen hours. Drug toleration appears to occur in some patients but in others toleration has been inconspicuous or absent.

Ordinarily there has been little if any effect on the pulse-rate. Bradycardia was observed in 2 patients 1 of whom showed a fall of pulse-rate from 72 to 54 per min. Several patients, however, showed slight increases of pulse-rate.

The taste and bulk of drug to be taken is a disadvantage in some patients but combination with hydrochlorothiazide and a small dose of reserpine, rescinnamine, or canescine may decrease the amount of bretylium tosylate required. A further reduction in bulk may be effected by substituting a small dose of one of the low-dose ganglion-blocking drugs. We have used pempidine tartrate (' Perolysen ') and M & B 4500, the latter being probably the most potent of the ganglion-blocking drugs with about double the activity of pempidine tartrate. This combination of a highly active ganglion-blocking drug with bretylium tosylate has been given in 9 patients with return of parasympathetic side-effects in 1 only. In two instances 3 mg. of pempidine was equivalent to 150 mg. of bretylium tosylate and in three instances 1 mg. of M & B 4500 was equivalent to 100 mg. of bretylium tosylate. If dosage is further reduced by the use of hydrochlorothiazide or rauwolfia alkaloid as mentioned above the occurrence of unexpected hypotensive episodes should be decreased. Unexpected hypotension has certainly been a more common experience in our patients with bretylium tosylate than in patients receiving the more potent ganglion-blocking drugs.

The majority of patients made no spontaneous complaint of side-effects from bretylium tosylate but direct inquiry elicited minor symptoms in several patients.

Those patients who have been given a trial on bretylium tosylate because of persisting parasympathetic side-effects from one or more ganglion-blocking drugs were all relieved of these symptoms. One patient, however, began to complain of great muscular weakness and insisted he was better on the ganglion-blocking drug M & B 4500. Nasal obstruction, mentioned by Boura et al.,[1] has been noted occasionally; undue sensitivity to cold, another result of decrease of sympathetic vascular tone, was mentioned twice. Looseness of the bowels occurred in 5 out of 33 patients, one having considerable diarrhœa which stopped when the bretylium tosylate was discontinued and started again as it was resumed. 1 patient, however, who had had diarrhœa previously, probably due to mild ulcerative colitis, was no worse on bretylium

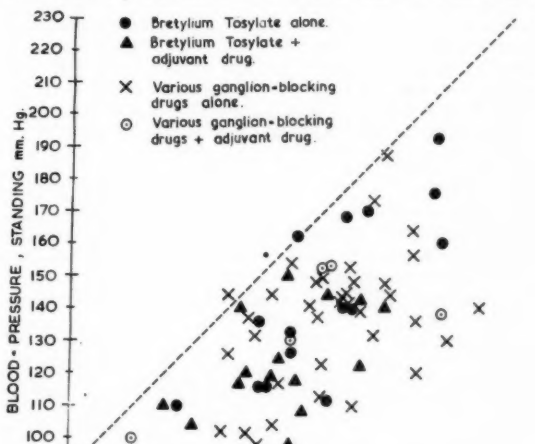

Fig. 2—Relationship of blood-pressures in the lying and standing postures in patients under the action of bretylium tosylate or various ganglion-blocking drugs.

1. Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., Rosenheim, M. L. *Lancet*, July 11, 1959, p. 17.

tosylate. Incidentally we found a small proportion of rats given 20 mg. per kg. developed unusually loose motions.

It should be kept in mind that reserpine decreasing as it does sympathetic activity without decreasing parasympathetic may lead to activation of peptic ulcer. While we have encountered some indigestion in two cases with bretylium tosylate there has been no suggestion of ulceration. It will be well to bear this possibility in mind. Combination with a ganglion-blocking drug should decrease any such risk.

It is of interest that although there were few spontaneous complaints several patients referred on inquiry to mild ocular symptoms. Heavy sensations about the eyes were mentioned by 4 and visual blurring, usually slight and transitory, was referred to by several patients. However, blurring disappeared in 2 patients on increasing the dose and persisted in 2 on omitting the drug. In 1, possibly 2, patients, however, we thought blurring might have occurred from the drug action.

Only 2 of our patients expressed a preference for their previous ganglion-blocking drug therapy.

Beyond question the new hypotensive agent bretylium tosylate is of great interest and provided long-term toxicity does not develop the absence of significant parasympathetic side-effects will make it the hypotensive agent of choice for many patients. When the dose is large this disadvantage is easily overcome in most patients, without return of parasympathetic side-effects, by replacing some of the tablets of bretylium tosylate by an equivalent hypotensive dose of one of the potent ganglion-blocking drugs.

We are indebted to the Medical Research Council of New Zealand for financial support and to the Wellcome Foundation Ltd. for generous supplies of bretylium tosylate.

Department of Medicine,
University of Otago Medical School,
Dunedin.

F. H. SMIRK
J. V. HODGE.

ACUTE ANHIDROTIC SYNDROME

SIR,—Dr. Bannister's syndrome (Sept. 12) is not peculiar to the tropics. The earlier manifestations are in fact quite familiar to many farm-workers here in the United Kingdom, who are especially liable to be affected during strenuous autumn harvesting. Like Kipling and his contemporaries, they too have for generations kept safety in the action of that excellent diaphoretic, hot tea.

These " dry sweats ", as some call the condition, follow a constant course of events. A worker already much heated by hard labour in the sun unwisely seeks comfort in drinking a great volume of chilly fluid; then, refreshed, hurries back into the glare to strive even harder than before. Quite soon his perspiration stops, and, if he is foolish enough to persist in his toil, headache, dizziness, and mild confusion possess him, while weakness and clumsiness render his state obvious to his wiser mates. Ignoring his now garbled talk, they lay the patient in cool shade and dose him with hot tea. Thus shortly the saving sweat breaks out and he is restored to health. Protection from this nuisance may be invited by quenching thirst with tea; or by taking cold liquids in quantities never sufficiently large to cause the chilling which discourages perspiration and seems usually to initiate the disturbance. From what these people have said I understand that taking extra salt does little or nothing towards averting an attack or increasing resistance.

This constant sequence suggests the mechanism of the process. Presumably the heat-regulating centre is misled by local visceral chilling and resets toward retaining body heat. Upon resuming intense activity heat is generated so rapidly in an already hot body, that the temperature has reached levels sufficiently high to completely upset the centre before it has had time to bring about adequate compensation. This has direct bearing on the tropical cases, for it is a common habit of new arrivals to try and cool themselves with great draughts of the coldest drink they can find, until eventually they learn that hot drinks, and particularly hot tea, are much more efficient to this end.

Dr. Bannister suggests that it is probable that the anhidrosis was the primary cause of heat exhaustion in his patients. This seems surely true, but I would offer that it is at least likely that acute anhidrosis is often in turn the result of internal chilling.

Group Pathological Laboratory,
Royal Hants County Hospital,
Winchester, Hants.

T. J. MUCKLE.

ACUTE PARENCHYMATOUS GLOSSITIS WITH GANGRENE OF THE TONGUE

SIR,—I would suggest temporal arteritis as the cause of the remarkable tongue gangrene in the patient described by Mr. Howard and Dr. Cremin (Sept. 19).

Their patient was elderly and she had five weeks of night sweats and pain in both temporal regions before the tongue became involved. If her terminal lingual arteries were bilaterally thrombosed the condition would seem to me analogous to the bilateral retinal-artery thrombosis which is also known to occur in arteritis.

Hillingdon Hospital,
Uxbridge, Middlesex.

D. WISE.

PATHOGENESIS OF THE ANÆMIA ASSOCIATED WITH HIATUS HERNIA

SIR,—I thank Dr. Jasinski for his observations [1] on our article.[2] I should like to add the following:

The purpose of my published work is to find the origin of hiatus-hernia anæmia for which no known cause exists.

We clearly stated that the usual cause, hæmorrhage, was absent and that repeated examinations of the fæces for occult blood were negative. The method we used for occult blood was Meyer's reaction, instead of the recommended benzidine test. In addition, endoscopic examination of the lower part of the œsophagus and of the prolapsed part of the stomach showed no lesion which could be responsible for hæmorrhage. If there was bleeding from some other part of the intestine, why did the patient's anæmia disappear after the operation?

My own experience and that recorded in the literature indicates that liberation of the herniated part of the stomach leads to complete resolution of the anæmia, without any other treatment. We are, therefore, absolutely convinced that the herniation is the chief cause of this kind of anæmia. Our research was seeking the relation between herniation and anæmia.

At first, we tested whether Fe^{++} could be absorbed by the patient and the result was negative. The same absorption was easily demonstrated in another patient suffering from post-hæmorrhagic hypochromic anæmia, but without hiatus hernia.

When Fe^{++} was mixed with the gastric juice of another normal person and given to our patient, iron absorption was readily restored. This forced us to accept that there is a factor in the gastric juice which facilitates the transformation and absorption of iron. Since the prolapsed part of the stomach in hiatus hernia is usually the fundus and a part of the body, we thought that the intrinsic factor which is secreted from these parts might be the factor we are looking for. In fact a mixture of Fe^{++} with intrinsic factor produced absorption exactly like that obtained with gastric juice.

After our article appeared, we had the opportunity to examine another patient in which the prolapsed part was not the fundus. The patient had had a gastrectomy. The hæmatocrit was 45%, the Hb 15%, and serum-iron 100 μg. per 100 ml.

As regards the rapid increase of hæmoglobin with intrinsic factor, the previous repeated administration of iron, for the performance of the tests, also contributed to this. But there is evidence that the administration of intrinsic factor (' Bendogen ') contributes to the treatment of any hypochromic anæmia.[3]

Finally, in pernicious anæmia, the serum-iron level is normal or slightly increased, despite the lack of intrinsic factor. In this case, we think that the coexisting hæmolysis may explain the

1. *Lancet*, 1959, i, 1100.
2. *ibid.* p. 552.
3. Tsevrenis Hip. Personal communication.

lack of iron deficiency. However, in some cases, where the hæmolytic factor does not obviously exist, an iron deficiency will certainly result. On the other hand, treating the disease with vitamin B_{12} or intrinsic factor quickly reduces the serum-iron level to below normal and the administration of iron becomes necessary.

Therefore, in my opinion, the whole subject needs further experimental research in order to demonstrate whether or not the theoretical chain of our thoughts can be confirmed.

Athens. G. I. MICHAELIDES.

BEDS FOR CONFINEMENT

SIR,—May I suggest that although the correspondence on this subject has dealt with most of the aspects, one essential has been overlooked—I mean the prima donna herself, the expectant mother.

In 1957, I carried out a survey[1] in the Salford area amongst expectant mothers to find out where they preferred to have their confinements and why. A great majority of primigravidæ preferred hospital: surprisingly, only 46% because of its "safety". As many as 47% were not satisfied with the conditions at their homes. 79% of the multigravidæ belonged to this group. In women preferring home confinement, over 70% preferred to "lie in" surrounded by their families and/or did not like the idea of stay in hospital. When asked in the postnatal clinic, if they would like to "book in" again, 78% said "no", although quite a few of these are bound to come again because of home conditions.

To me it seems quite clear that at least in this part of England expectant mothers have voted quite convincingly in favour of a "maternity home" for confinement only, and "lie in" at home if all goes well, as in fact was suggested by Sluglett and Walker,[2] and of course in your annotation of Sept. 19.

Department of Obstetrics and Gynæcology, Hope Hospital, Salford. U. N. PATHAK.

IMIPRAMINE

SIR,—We wish to record two further examples of excessive stimulation as an occasional side-effect of the antidepressive drug imipramine ('Tofranil'), similar to those described by Dr. Brooke and Dr. Weatherly (Oct. 10).

CASE 1.—A married woman, aged 24, appeared to have taken between fifty and fifty-six 25 mg. tablets—i.e., at least 1250 mg. She showed signs of cerebral irritation, with jerky movements of eyes and limbs, general restlessness, and distractibility. Although she was able to make slight conversation and was correctly orientated, she was unable to give an account of herself. The interview was terminated by a grand-mal convulsion. Following this, examination of the nervous system revealed extensor plantar responses, but otherwise no abnormality. She had a total of three major fits during the day of admission and was treated with intramuscular and oral paraldehyde until her condition improved.

CASE 2.—A man, aged 83, received imipramine in gradually increased doses up to 75 mg. t.d.s. over a period of two and a half months. After thirteen days at this dosage level he showed signs of excessive stimulation, being hyperreactive to stimuli both physically and mentally. He showed muscular hyperirritability, jumped at any touch or sound, and showed acceleration of thought and a jerky rapid speech. The imipramine was stopped, and at the end of three days these symptoms had subsided completely.

Both patients were receiving treatment for endogenous depression, that in the first being associated with the puerperium, and that in the second being of the late involutional type.

We do not consider that these cases of excessive stimulation detract from the general usefulness of imipramine in depression (particularly endogenous), and indeed, together with our colleagues at this hospital, we have found it to be extremely useful.

Cherry Knowle Hospital, Ryhope, nr. Sunderland. LESLIE J. LEVENE
C. F. LASCELLES.

PROPHYLAXIS IN ISCHÆMIC HEART-DISEASE

SIR,—Dr. Barnes's excellent paper (Aug. 22) raises two points: the first is concerned with the ætiology of atheroma, and the second with the risks of thyroid treatment.

In support of his rationale for the prevention of ischæmic heart-disease, Dr. Barnes might have advanced still more evidence. He might have mentioned the fact, for instance, that shortly after Anitskoff produced atheroma in rabbits by cholesterol feeding, attempts were made to bring this about in dogs. These were unsuccessful until Steiner et al.[1] in 1949 added thiouracil to the cholesterol feeds. Atheromatous lesions were then produced indistinguishable from those occurring in man.

Attention might also have been drawn to the relative immunity to coronary thrombosis enjoyed by women during the childbearing period. It is difficult to dissociate this fact from increased activity of the thyroid gland when we recall the results of certain animal experiments and correlate these with the corresponding facts of human physiology. The continued injection of œstrogenic substances into rats and guineapigs is followed by thyroid enlargement while castration is followed by reduction in its size.[2] In women the thyroid enlarges at puberty, it enlarges in relation to menstruation, and it enlarges during pregnancy. Myxœdema, predominantly a disease of women, usually appears at the menopause or just after it—at a time when one would expect an inherently weak thyroid to begin to peter out. Extreme degrees of atheroma have been repeatedly demonstrated at necropsy in myxœdema, while atheroma is absent in Graves' disease.

We have heard a great deal recently about the importance of an excessive intake of fat (unsaturated fatty acids) in the causation of atheroma. This is reminiscent of early views on the cause of diabetes mellitus, which was attributed to excessive intake of starch and sugar. Only when the part played by insulin in carbohydrate metabolism was discovered did the role of the dietary factor come into proper focus. It seems that history is repeating itself and that the answer to the present problem will once again be found at the endocrine level.

I agree with Dr. Barnes that the dangers of thyroid treatment have been much exaggerated. The reason for this is not far to seek. It lies in the fact that a number of deaths under thyroid treatment have received no adequate explanation. I cannot agree that these catastrophes are due merely to high dosage. I feel they are attributable to high dosage *or* a dosage that is relatively high only in special circumstances.

The truth of the matter was brought home to me when, after deciding that thyroid lowered the blood-pressure, I undertook the treatment of 50 hypertensives[3] in a pilot experiment. Wishing to make sure that all would receive adequate amounts of thyroid, I decided arbitrarily on a dose of gr. 5 per day. Among those receiving this dose were 2 patients with angina of effort. They came to me before the stipulated 2 weeks complaining that they were very much worse. Both stated that their attacks were more frequent, more readily induced,

1. Pathak, U. N. *Brit. J. clin. Pract.* (in the press).
2. Sluglett, J., Walker, S. *Lancet*, 1956, i, 684.

1. Steiner, A., Kendall, F. E., Bevans, M. *Amer. Heart J.* 1949, **38**, 34.
2. Best and Taylor's Physiological Basis of Medical Practice; p. 775. London, 1950.
3. Menof, P. *S. Afr. med. J.* 1950, **24**, 172.

and very much more severe. In both the diastolic pressure had fallen by about 20 mm. Hg.

As the filling of the coronary arteries is largely dependent on the level of the diastolic pressure, it was easy to explain what had occurred here. A larger dose or narrower coronaries might well have precipitated a myocardial infarction. I have no doubt that most of the unexplained deaths under thyroid treatment (nearly all of which occurred in cases of myxœdema) were due to sudden coronary insufficiency or myocardial infarction. That high dosage in the absence of coronary narrowing is unattended by any risk is the conclusion I have reached after many years' experience in the use of this hormone.

Thyroid, then, should be given with care in angina and in all who have had a coronary thrombosis. Because of my early experiences, I regarded such evidence as an absolute contra-indication to treatment. Recently, however, I decided that it would be justifiable to treat hypertensives having angina with smaller doses. The fall in the diastolic pressure would not be so precipitous and it would thus be possible to gauge the level at which the diminution in coronary blood-supply would be more than compensated for by the diminution in the work of the heart.

To date 5 such cases have responded favourably to this approach. In a 6th case in which there was no hypertension the angina had reached the stage of decubitus. Here the underlying cause was xanthomatosis tendinosum associated with hypercholesterolæmia. A daily dose of gr. 2 reached by weekly increments of gr. $^1/_2$ daily on an original dose of gr. $^1/_2$ daily enabled the patient after 2 months' treatment to carry on normal activities without pain.

One can only hope that further work will confirm these results and those obtained by Dr. Barnes.

Johannesburg. PERICLES MENOF.

CANCER AND THE CENTRAL NERVOUS SYSTEM

SIR,—In their exceptionally interesting article on the neurological syndromes associated with carcinoma Sir Russell Brain and Dr. Henson [1] pointed out that the disease process in the nervous system does not necessarily parallel the duration or the size of the tumour. These observations prompted the idea that some primary functional change in the central nervous system may have a fundamental significance in the origin of human cancer.

The first piece of evidence for this hypothesis seemed to be the determination of the concentrations of acetylcholine and noradrenaline in the central nervous system and cerebrospinal fluid (C.S.F.) of patients with cancer.

Because of technical difficulties I had to limit my own investigations to determining the concentration of true cholinesterase in the C.S.F. The technique developed by Stedman et al.[2] for measuring true cholinesterase in serum was used, except that *N*/1000 was substituted for *N*/100 sodium hydroxide.

In 35 control cases (15 healthy subjects and four groups of 5 patients with acute inflammation, hypertension, congenital heart-disease, and cholelithiasis), C.S.F. true cholinesterase measured between 8·0 and 12·0 units (average 9·4). On the other hand, in 29 of 30 patients with histologically proven cancer in widely different sites, the figures were lower and ranged between 3·8 and 7·6 units (average 5·8).

Serum-cholinesterase in cancer patients, however, was not necessarily different from that of controls. From results in more than 100 patients with various mental or liver diseases, I am certain that the levels of cholinesterase in the serum and C.S.F. are independent of one another—perhaps because the main site of cholinesterase production is in the ganglion cells of the central nervous system.

Because of this reduced cholinesterase concentration, activity in the ganglia might possibly be increased. Consequently any lesion affecting the epithelium and causing afferent impulses to pass to the spinal cord might provoke greatly increased efferent impulses tending to bring about hyper-regeneration. In later life this reflex arc might be more constantly invoked and, if the energy of the epithelium became exhausted, processes leading to maldevelopment and the development of tumours might occur.

In the precancerous phase the interruption of such a segmental reflex arc by drugs or physical treatment (for example, by electric shock) might prevent this development of tumours.

1. Brain, W. R., Henson, R. A. *Lancet*, 1958, ii, 791.
2. Stedman, E., Hall, G. E., Lucas, C. C. *Dtsch. med. Wschr.* 1956, **80**, 1959.

County Hospital, Gyula, Hungary. BÉLA HERMAN.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—In your issue of Oct. 10, Dr. Macdonald and Dr. Sharman describe a test using the cervical mucus, which by its very simplicity could be of great use to the general practitioner if it proves to be reliable. But in the final paragraph of their letter they say: "The test is less valuable to the average busy practitioner since a vaginal speculum examination is required". This does reflect a most regrettably low opinion of general practice. I should like to think that it is in fact quite unjustified, and that the routine use of a vaginal speculum in ordinary general practice is a great deal more usual than their opinion implies.

Great Dunmow, Essex. GEOFFREY BARBER.

BLOOD-GROUPS

SIR,—In a symposium recently published in England [1] many of the leading British investigators presented their most recent work on blood-grouping. In view of their highly specialised nature, this group of papers will probably be of interest chiefly to workers in the field. Unfortunately, however, the presentation is slanted almost entirely to the contributions and views of British workers, and does not do justice to the findings of pioneering American investigators. As a result, the articles are not only incomplete but also contain serious errors and misinformation that destroy the usefulness of the volume, except for those few critical workers who are capable of discriminating between the facts and fallacies which it contains.

One of the outstanding faults of the volume derives from the continued use of the Fisher-Race C-D-E notations in the face of overwhelming evidence of their numerous fallacies. These notations teach triple inheritance of Rh-Hr genes and agglutinogens even though a gene such as R^{1w} has been shown to give rise to an agglutinogen Rh_1^w with the blood factors **Rh$_o$**, **Rh^A**, **Rh^B**, **Rh^C**, **Rh^D**, **rh′**, **rh$_1$**, **rh^w**, **hr″**, and **Hr$_o$**—a total of ten factors instead of three. As Wiener [2] has demonstrated, the number of blood factors characterising an agglutinogen depends in large degree on one's industry and ingenuity in searching for and finding blood-grouping antibodies of new specificities. Thus, the main issue at stake here is on a serological level and not on a genetic level. Moreover, the linkage theory credited to Fisher was not original with him, since Wiener [3] published an analysis of the theory two years before Fisher entered the picture. Fisher merely elaborated on an erroneous idea that Wiener had previously disproved and discarded. The symposium includes no reference to the recent detailed and well-documented report [4] of the Committee on Medicolegal Problems of the American Medical Association, in which it is recommended that C-D-E notations be discarded, and the Rh-Hr Nomenclature be used exclusively.

Again, much space is given to studies on blood-groups and disease—a different kind of blood-group paradox also inspired by the biometricians. Of course, the clinical importance of

1. *Brit. med. Bull.* 1959, **16**, no. 2, pp. 89–174.
2. Wiener, A. S. *Science*, 1958, **128**, 849.
3. Wiener, A. S. Blood Groups and Transfusion; p. 254. Springfield, Ill., 1943.
4. *J. Amer. med. Ass.* 1957, **164**, 2036.

blood-group incompatibility in erythroblastosis is well known, and here the selective value of the blood-groups has been clearly established. However, no explanation has been advanced as to how or why group O should lead to ulcers, group A to fractured femurs, non-secretor type to rheumatic fever, &c. Evidently, these workers have not carefully considered that Nature is reasonable, or the role which statistical chance and bias in collecting the data might have played in their findings. For example, the use of so-called universal donors in emergencies for patients admitted to hospitals with bleeding ulcers could give rise to the erroneous impression, when analysing the records, that more patients were group O than was actually the case. Such studies have no rationale and are doomed to failure. In fact, this line of research was very popular thirty years ago, but was abandoned when it was found that such studies do not yield any significant results.

In conclusion, the defence of the use of the C-D-E symbols on the grounds that they are simple and easy to understand is not worthy of a mature scientist. Paradoxers "understand" simple things that are untrue, but competent scientists can understand facts and principles and terminologies based on such facts, no matter how intricate, so long as they are correct. Because this collection of papers continues to place simplicity above accuracy, it will do damage instead of advancing the subject.

New York. A. S. WIENER.

"PRECORDIAL CATCH"

SIR,—It is with great reluctance that I further muddy the waters of nomenclature so well described in Dr. Asher's article of Sept. 19.

In his article he refers to "a pain without a name": a brief sharp pain near the apex of the heart and aggravated by deep respirations. This pain, happily or unhappily, *has* been given a name. It was labelled the "precordial catch" by Albert Miller and Teodoro Texidor.[1]

They state that the syndrome has three major aspects:

"1. All the patients have been light or median body build; they have been below the age of 35 years, and there has been no particular sex incidence.

2. The pain is severe, sudden in onset, does not radiate, and is regularly located near or above the cardiac apex.

3. The pain occurs at rest or during mild activity and is frequently related in onset to a 'slouched' posture."

Fortunately the name implies no ætiological significance and requires no knowledge of Latin.

Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. FRANK OSKI.

THE DANGERS OF STOPPING LONG-TERM ANTICOAGULANT THERAPY

SIR,—Recent papers have agreed that long-term anticoagulant treatment is of some benefit to patients who have had a cardiac infarction, but the dangers of stopping this treatment do not seem to have been stressed. In the past three years, 36 patients under my observation have stopped anticoagulants after more than three months' treatment; 6 had further thrombotic episodes while tailing off the dose or within a week of stopping. It is not always possible to carry on anticoagulants indefinitely either because of complications or potential complications, such as peptic ulcer, or because laboratory facilities are not available for the very large number of patients which would accumulate after a few years. When starting such treatment it would be wise to consider that it may be dangerous ever to stop.

Ashford Hospital, Ashford, Middlesex. M. J. D. NEWMAN.

1. *J. Amer. med. Ass.* 1955, **159**, 1364

THESAUROSIS FOLLOWING INHALATION OF HAIR SPRAY

SIR,—I feel I must reply to some of the points Dr. Edelston raises in his letter of Sept. 26.

Firstly I must apologise for my error with regard to the time of exposure and the development of symptoms. In my letter of Sept. 19 I stated that no skin test had been performed to support the diagnosis of thesaurosis. I was aware that a tuberculin test had been carried out but the fact that this was positive is neither evidence for nor against the diagnosis of thesaurosis. In the same issue of *The Lancet* as Dr. Edelston's report, there is an excellent leading article on berylliosis. In this reference is made to a case of berylliosis described by Dr. I. Sneddon and of the ingenious method of skin testing he applied to confirm his diagnosis. I feel Dr. Edelston could have applied the same principle in his case. There are other skin tests that should be performed, in the absence of biopsy evidence, in any granulomatous disease of the lungs, including the histoplasmin and Kveim tests. Histoplasmosis has been described more frequently in England than has thesaurosis.

Lastly, I must confess I have been more fortunate than Dr. Edelston and have seen several confirmed cases of sarcoidosis with a positive tuberculin test. Two of the leading authorities in Great Britain on this disease, describe large series with around 30–40% of cases reacting to tuberculin. Thus James [1] describes 40% of his series of 200 cases having a positive reaction to tuberculin. Likewise Citron and Scadding [2] describe 49 patients with sarcoidosis of whom 21 reacted to tuberculin and 6 reacted to 10 units or less.

Section for Pulmonary Diseases, School of Medicine, University of Maryland, Baltimore W. K. C. MORGAN.

DOMICILIARY REHABILITATION OF THE RESPIRATORY CRIPPLE

SIR,—Recently when in Denmark I had the opportunity and very great privilege of seeing the remarkable achievement of the Danish Government health authorities and the voluntary agencies concerned with the care of those severely disabled as the result of the epidemics of poliomyelitis. I was particularly impressed by the steps taken to rehabilitate within the home the few patients still remaining with severe respiratory paralysis. One such I saw through the kindness of Dr. Hans Lou and Dr. Ingebor Lou in Kolding, Jutland. The patient, a man of about 45, had been a small farmer but in 1953 was stricken with very extensive poliomyelitis of almost complete tetraplegic distribution. There remained entire respiratory paralysis and the only peripheral recovery was of a few flexor muscles in the fingers of the left hand. In the earlier stages the man had been a severe psychological problem. Now he is no longer *existing* but is living a life of complete psychological adjustment and reasonable happiness.

The steps which had been taken were briefly as follows:

With his own small savings and a considerable Government grant a specially designed bungalow had been built for him and his family of wife and child. The wife was paid a salary by the Government as a nursing assistant and her work was reinforced by the part-time help of two trained nurses. His bed was freely mobile from one room to another, particularly the bathroom in which there was a special hoist for lifting him in an out of the bath. The bedroom was provided with all the fitments required for attachment to the electrically controlled breathing apparatus which was attached to a tracheostomy tube. In the bedroom were conveniently placed such things as television apparatus, and in fact it was equipped like any good hospital private room. During bed treatments it was possible for the patient to exist for half an hour, without the breathing apparatus, by using

1. James, G. *Quart. J. Med. N.S.* 1958, **28**, 109.
2. Citron, K., Scadding, J. G. *ibid.* 1957, **28**, 277.

a basic respiratory function through glossopharyngeal activity (frog breathing). He also had been provided with a special type of invalid chair in which he could sit and in fact be wheeled into the town to visit his friends, the chair having behind the seat an oxygen controlled breathing apparatus of Swedish design, which enabled him to be free of his electrically controlled apparatus for up to about four hours.

The whole affair was most impressive. Although the cost of the bungalow and of the maintenance by three part-time paid individuals must be very considerable yet it was clear that this was greatly less than would be the cost of treating such an individual in a hospital or other institutional bed. Furthermore there was no doubt that here was a family unit, living as such in as near as possible a normal manner, having in mind the extreme severity of the patient's disability.

In Great Britain there are still a number of such people with severe respiratory paralysis. Institutional care appears to be the only method available for treatment. It would seem to me, however, that we have much to learn from the Danish method and that the Ministry of Health should go into this question very thoroughly before developing permanent institutional accommodation, which would be both highly expensive to maintain and for the patients a comparatively unhappy solution.

Exeter. NORMAN CAPENER.

THE MECHANISM OF MIGRAINE

SIR,—I read with great interest Dr. Hamilton's letter of Sept. 19. As long ago as 1932 I suggested that alkalosis could promote vasoconstriction, the first phase of the vascular mechanism of migraine. I did so in a paper which I was invited to read on the subject of the Vascular Theory of Migraine [1] before the German Society for Internal Medicine and Neurology in CSR.

Leicester. LEO HAHN.

CANCER: TO TELL OR NOT TO TELL?

SIR,—Doctors forget that in nine cases out of ten their intelligent patients have done a lot of hard thinking before they come to them at all about their fears. Wisely or unwisely they have probably read up their symptoms. When they are told they must have an operation they may not ask any awkward questions but they think the more. This is where far greater skill than is required for diagnosis comes in, and where so many doctors unwittingly fail their patients. If things go seriously wrong and a patient complains the first defence of the medical profession is that doctors cannot be expected to be infallible. Yet how many times do they adopt that attitude without any justification? Personally I have yet to meet the patient who expects infallibility from a doctor. The pendulum has swung in the opposite direction. But they do hope for better understanding and imagination. Is it not then a mistake for doctors to think they have the right to give any verdict which to ordinary mortal minds spells death? Or to hide from a patient something which he or she may know or guess or worry about inwardly? The surgeon is at a disadvantage because he seldom knows his patient personally. But the family doctor should and must accept that responsibility when attending a patient with serious illness. He can then be the human link between his patient, the surgeon, and hospital staff. But how often does this work out? Far too little is known about the patient as a human being.

I well remember a woman in hospital at the same time as I was some years ago. I was just on my feet again when she had her operation, and I tottered over to her when I heard her ask for a drink and was told she could have one. Lifting her head with my hand I held the feeding-cup to her lips and I shall never forget her agony until she had brought back that small drink. She had asked the ward sister what had been done. The sister, a kindly woman but unprepared for the question, said, "We see many sad things in our life, but . . ." and in so many words she told her to make the best of what time she had left. Struggling to tell me this she said, "I am ready to die but . . ." The tears streamed down her face and vomiting prevented her saying more.

I am only a lay person but is it not possible to be prepared for such moments and to give a merciful shot in the arm that will give peace and sleep to a patient until she is able to be talked to properly and privately by someone equal to the responsibility?

When I was young I heard a sermon once on the problem of pain. The Minister finished by saying "Perhaps some of you are thinking 'but what does he know of what I have been through'. Well, if that is so I can only tell you that you have a qualification that I may for ever lack . . ." A patient's body is his own as is his mind and soul, and no-one is qualified to give him or her a final verdict on anything. A doctor would be far better advised to try more humbly to make contact with those minds and be willing always to learn from them—yes, even when it conflicts with those textbooks! To suffer deeply is to enter a hitherto unknown world, an experience that often deepens perception in a way that is infinitely more valuable than mere technical or academic knowledge. We seldom find people who have truly suffered in mind, body, or spirit, offer hard and fast opinions or verdicts. They tread softly. There is an old Chinese proverb: "To know what you know is good. To know what you do not know, that is wisdom."

Braunton, Devon. WINIFRED CUMMINGS.

ÆTIOLOGY OF PULLORUM DISEASE AND FOWL TYPHOID

SIR,—In your annotation of Oct. 3, The Convalescent Excreter of Salmonellæ, a sentence begins: "In bacillary white diarrhœa of chicks and in fowl typhoid (both due to *Salmonella gallinarum*) . . ."

We recently published [1] an account of the study of 1007 cultures of *Salmonella pullorum* and 618 cultures of *Salmonella gallinarum* isolated from poultry between 1950–55. We considered that our results taken in conjunction with the work of a number of earlier investigators provided conclusive evidence that *S. pullorum* and *S. gallinarum* are separate and distinct species, the former causing pullorum disease (B.W.D.) and the latter fowl typhoid.

We draw attention to our work merely because your annotation presents a contrary view as a fact rather than as a matter on which there are different opinions.

Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food, Weybridge, Surrey. J. D. BLAXLAND. W. J. SOJKA.

X-RAY REPORTS

Dr. E. R. N. GRIGG writes:

"I am collecting documents on X-ray reports—those somewhat ephemeral texts in which the rœntgenologist lists and interprets the findings elicited during diagnostic examinations. Literature is relatively scarce, and bibliographic indications (perhaps reprints) in any language would be of help. Quotable sentences on what should or should not be included in X-ray reports are also invited. Most of all, I should like to receive originals of X-ray reports, in any language, dated prior to 1910, or more recent ones, if signed by renowned radiologists. In-

1. Hahn, L. *Med. Klinik*, 1932, **28**, 1264.

1. Blaxland, J. D., Sojka, W. J., Smither, A. M. *J. comp. Path.* 1956, **66**, 270.

cidentally, does anybody know who wrote the first X-ray report? The original reports, after being photographed for possible reproduction, will be returned to the sender if so desired, or else retained for an exhibit. My address is Box 293, Champaign, Illinois, U.S.A."

Obituary

JOHN WILLIAM ALEXANDER HUNTER

M.D. Edin., F.R.C.O.G.

Mr. John Hunter died on Oct. 10, a few weeks after he had retired from the active staff of St. Mary's Hospitals, Manchester, on reaching the age-limit.

When he graduated with honours at the University of Edinburgh in 1921, he was slightly older than the average student because he had served for four years in the Royal Field Artillery. He spent his early apprenticeship in obstetrics and gynæcology at Edinburgh Royal Infirmary and the Royal Simpson Memorial Hospital. In 1923 he moved to Manchester, where, as resident surgical officer to St. Mary's Hospitals, he came under the influence of Donald and Fothergill.

In due course Hunter was appointed to hospitals throughout the city. He was honorary gynæcologist to the Northern Hospital and to the Jewish Hospital, obstetrician and gynæcologist to Withington Hospital, and obstetrician and gynæcologist to St. Mary's Hospitals. His gift of clear exposition made him an excellent postgraduate teacher. His reputation was not confined to the British Isles, and he was held in high regard overseas, particularly in the United States. The film which he made of the Fothergill operation was originally presented by invitation at the International Congress of Obstetrics and Gynæcology in Paris in 1952. It has since been shown widely, and is still regarded as an unusually good presentation of surgical technique.

W. I. C. M. writes:

"As a gynæcological operator Hunter was meticulous. As an obstetrician he was conservative. His judgment was outstanding. He continuously strove after perfection. He demanded a high standard of dexterity from his assistants, and any failures on their part were rebuked sharply. He had indeed some of the qualities of the martinet, but his complete absence of malice disarmed resentment. He did not in any way exempt himself from self-criticism. To him, any failure to achieve perfection was a mistake. He would not compromise. As a result, the weight of worry which he bore was at times very heavy.

"He has left a name behind him by which his praises will be reported. More important, he has left nicknames. In his youth at Edinburgh he was invariably referred to as Derby Hunter. He was certainly born in Derby, though his family came from Aberdeenshire. In Manchester, the affectionate diminutive of John Willie was applied to him, sometimes in his presence. He was not an easy man to tease, often sheltering behind a prickly and pugnacious exterior when the attempt was made. This was a facade, behind which there sheltered a man shy, kind, hospitable, and generous to a fault. Many people and causes have good reason to acknowledge his generosity, though Hunter himself was invariably reticent about his good works.

"His recreations included motoring, at which he was in his prime a Jehu, flying, rock-climbing, and above all fishing. A member of several English fishing clubs, his chief joy was on the great Scottish rivers. Spey, Dee, Naver, Tay were equally well known to him, though in later years it was the last-named which was his favourite. When his senior colleagues at St. Mary's Hospitals took farewell of him at dinner shortly before his retirement, the menu was decorated by a snapshot of John Willie Hunter holding in either hand a magnificent fish, killed on his favourite beat near Stanley a few years ago. It is thus we shall remember him."

Notes and News

THE HEBERDEN SOCIETY

At a meeting of the society on Oct. 2 at the Postgraduate Medical School, Hammersmith, Dr. B. W. D. Badley and Dr. B. M. Ansell described an inquiry into the importance of steroid therapy as a predisposing cause of fractures in Still's disease. 216 patients with Still's disease, treated at the Canadian Red Cross Memorial Hospital, Taplow, were reviewed. 25 children had sustained 33 fractures, on 19 occasions following a definite episode of trauma. Of these 25 children, 9 were on maintenance steroid therapy in a daily dose of between 25 and 100 mg. of cortisone or its equivalent. A high proportion of the fractures were in girls in whom the disease had begun before the age of 5 years, and in whom it had been particularly severe. 5 patients on maintenance steroid therapy developed crush fractures of the vertebral bodies, without any antecedent history of trauma. More than half the 25 patients who sustained fractures had at some time had a period of complete bed rest for three months or more.

A paper by Dr. A. St. J. Dixon, Dr. J. T. Scott, and Miss D. Rix pointed out that several drugs were known to elevate serum-urate levels and to depress uric-acid excretion. Both pyrazinamide, an antituberculous drug, and chlorothiazide, an oral diuretic, had been indicted as having produced acute gouty arthritis. Detailed observations on a patient who developed hyperuricæmia and acute gouty arthritis during pyrazinamide therapy were presented. The hyperuricæmic effect of pyrazinamide was more effectively suppressed by small doses of aspirin than by large doses of probenecid. The difficulty in explaining these findings by conventional theories of uric-acid excretion were discussed, and one suggestion was that there may be at least two sites in the nephron where urate transfer could be modified.

Dr. Scott, Dr. Dixon, and Prof. E. G. L. Bywaters had reviewed some biopsies in a rheumatology unit. Skeletal pain due to metabolic bone disease might cause a patient to be referred to a rheumatism clinic. Biopsy was a valuable investigation in the diagnosis of these bone diseases, and the techniques of iliac-crest biopsy with the Nordin-Sacker needle under a local anæsthetic, and the preparation of both decalcified and undecalcified specimens, were described. This procedure was particularly valuable in the diagnosis of osteomalacia. It appeared that pain was not necessarily related to the histological finding of osteomalacia; that osteomalacia could itself cause an elevated sedimentation-rate; that osteomalacia may exist in the absence of accepted biochemical and radiological evidence; and that osteomalacia may cause or aggravate arthritis of weight-bearing joints.

Dr. Ansell and Professor Bywaters examined the concept of "palindromic rheumatism" as a separate clinical entity characterised by multiple attacks of acute or subacute joint pains, subsiding completely. They had studied 28 patients who fulfilled these criteria and were either at the Hammersmith Hospital or at Taplow between 1948 and 1956. 18 of these patients now had a definite chronic polyarthritis, with a positive differential agglutination test in 13, and nodules in 10. They considered that palindromic rheumatism was merely a variant of rheumatoid arthritis, and that the majority of such patients, if followed long enough, would eventually show residual signs of rheumatoid disease. The follow-up must sometimes be very long, and one patient's disease remained in the palindromic phase for twenty-four years.

The tradition of the Heberden Round is now established as an opportunity for clinical presentation of patients with rheumatic disease, and the 1959 round was conducted in lively fashion by Professor Bywaters, who took as his theme "the seven ages of man in rheumatoid arthritis". The round illustrated the incidence, symptomatology, and course of the disease from the cradle to the grave. He spoke appreciatively of the help he had received over the years from assistants and collaborators at Hammersmith Hospital and at Taplow. Evidence was presented to support the concept of a common

identity between the juvenile and adult forms of the disease, and the rigidity of classifications which excluded some patients with apparent rheumatoid lesions was criticised. The final demonstration was an excursion into the neighbouring province of geriatrics: a 20th-century octogenarian who previously suffered from rheumatoid arthritis was now in complete remission, " sans arthritis " but plus every faculty.

FORCES IN PHYSIOLOGY

THE lowest objective of those who teach physiology is to enable the student to understand something of the body's working in disease; their highest aim is to produce a trained research-worker: and between these two stools they often fall heavily. Sir Lindor Brown, Jodrell professor of physiology at University College London, made this observation when he was taking a look, on Oct. 14, at physiology, medicine, and the basic sciences in his opening address to this year's series of lectures on the Scientific Basis of Medicine, arranged by the British Postgraduate Medical Federation. In five short terms they had to construct the tottering edifice of knowledge that modern medicine desired. The few students who, by assiduity, brains, or good fortune, succeeded in that monstrous trial of endurance, the 2nd M.B. examination, might go on to further study for a B.SC. degree, and they formed a class that it was a privilege to teach. Reflecting on the relevance to medicine of preclinical teaching, Sir Lindor concluded that medical applications were useful means of softening hard facts, but they must be used very carefully. What was really needed was better physiologists to give better instruction in proper attitudes of mind. The expert teacher's job began when the student found out that the broad view which might be put to him in lectures often differed from what the textbook said. Looking forward, Sir Lindor saw that good young physiologists in this country would stay good only if they could spend more time on research work and travel and not too much on teaching of the intellectually unrewarding kind. Much more technical help was also needed.

The biochemical bandwagon showed signs of overcrowding and might be slowing down, but the biophysical one was just beginning. Physiologists of the future might turn round and say, as Sir Henry Dale put it, " There's old Dale: he once used a smoked drum "; but, Sir Lindor hoped, it might again be demonstrated that " smoked drum and brains " could still achieve much.

AN AUSTRALIAN ENTERPRISE

A NEW approach to medical education and research was made last year when the University of Sydney set up its Post-Graduate Medical Foundation.[1] This is essentially an association of citizens who, recognising the importance of certain medical activities, are establishing a fund to enable the university to carry them out. But the first report, by Dr. V. M. Coppleson, the director, in collaboration with Prof. Bruce Mayes, dean of the faculty of medicine, shows that its role is widely conceived.

One purpose is to give the university some of the money it needs for special equipment and personnel; and substantial grants have already been made to Sydney investigators for research both at home and overseas. The university is being helped with " the speeding up and introduction of new methods, knowledge and techniques in medicine into Australia ". But the Foundation is itself to be a channel for the dissemination of some of this new knowledge, and the organisers are putting into practice their belief that postgraduate medical education can no longer be confined to the medical profession.

Among the grants already made are a number enabling visitors from other countries to lecture or work in Australia.

Lecturing on the care of the subnormal and physically handicapped child, Dr. L. T. Hilliard, of the Fountain Hospital, was able to address not only doctors but also social workers, parents, and citizens of Sydney and Newcastle, and arrangements were made for him to go on to other Australian States and to New Zealand. Dr. Austin Eagger, of Slough, was enabled to meet leaders of industry and labour in New South Wales. The Foundation has been interested in the visits of Prof. R. M. Kark and Prof. Jethro Gough, and on its invitation Dr. L. G. Norman, of London Transport, is to be in Australia and New Zealand from Oct. 19 to Dec. 14, discussing medical aspects of the prevention of road accidents. Other prospective visitors from England include Prof. P. C. Koller, Dr. Peter Alexander, and Dr. C. E. Ford, who is to spend some six months in Sydney as a guest worker on mammalian chromosome techniques.

1. *Lancet*, 1959, i, 143.

CHANGES IN PSYCHIATRY

FOUNDED at York in 1796, The Retreat is a mental hospital which remains outside the National Health Service. Last year the average number of patients in residence was 236, and in his annual report as physician-superintendent Dr. Cecil Beresford notes that in nearly every form of psychiatric illness " we are admitting with increasing frequency the atypical case, probably because the absolutely straightforward illness is now often treated as an Outpatient, or in the psychiatric department of a General Hospital ". Speaking of the great improvement in psychiatric services in the past few years, he welcomes the steady (though slow) improvement in aftercare services, which should be even more manifest when the Mental Health Act comes fully into action. But he sees " one little danger " which such an improvement can increase:

" The widespread and serious overcrowding that obtains in nearly every State Psychiatric Hospital does make it important to get the patient out again as soon as possible. Sometimes it is too soon, and the knowledge of an efficient After-care Service could encourage such a too-early discharge. It is necessary to make the point that After-care is rightly the supervision of a recovered person, to help him to rehabilitate and do everything to minimise the risk of further breakdown. Too often it is expected to accept the half-recovered person and help him to adjust more or less satisfactorily to the demands of life outside the hospital. Someone in such a situation can often suffer or cause others to suffer far greater unhappiness than anyone should really be expected to bear."

University of London

At recent examinations for the D.C.P. the following were successful:

Victor Blackman, Ramon Abad Custodio Lopez, P. W. Edmondson, Paul Grasso, F. R. Jones, W. N. Laing, P. F. A. Milner, Sanatkumar Mitra, Satyendralal Mitra, Abdul Salam Mohamed, Hla Myint, Sangarappillay Sivalingam, Julius Suskin, Sachendra Prasad Varma, B. M. Wadham, D. S. P. S. V. J. Wijesekera.

University of Wales

The following degrees have been conferred:

M.D.—W. H. Beasley.
M.Ch.—L. P. Thomas, E. M. Williams.

Royal College of Obstetricians and Gynæcologists

At the annual dinner, held in London on Oct. 16, Lord Twining was the guest of honour. Prof. Andrew Claye, the president, reported further progress with the new building in Regent's Park, which is to be officially opened on July 13, 1960. He reminded all associated with the college—in Britain and the Commonwealth—that funds were still needed urgently. Dr. J. Bruce Dewar proposed The Guests, and Lord Moynihan responded.

At the meeting of council on Oct. 16 with the President in the chair, the following were admitted to the membership:

R. M. Adam, Margaret A. Austin, Debabrata Bhattacharyya, Sridevi Biswas, Basil Bloch, Audrey A. Boutwood, M. D. Cameron, Aseem Parkash Chakravorty, Srinivas Krishnama Char, David Charles, Sunil Kumar Chaudhuri, Ellis Cooper, J. D. Crowley, I. J. Dalrymple, Kaushlya Dodeja, D. A. S. Eddie, E. J. Esler, Jill M. Evans, W. D. Fraser, Srasht Kumari Ghai, Aloka Gupta, J. D. Hehir, Alexander Herriet, B. J. H. Insull, Chelliah Kathirkamanathan, Tye-Hin Lean, Sydney Lubert, R. H. Lumer, R. R. Macdonald, Kathleen McKee, Hugo McVey, Sanat Kumar Mandal, A. W. Maxwell, C. D. Moloney, Kamala Mukherjee, Margaret H. Murray, C. J. B. Orr, Olga M. Rampersaud, J. A. Riedel, J. G. Robertson, M. L. Robinson, D. W. A. Rodwell, Nagendra Nath Roy Chowdhury, C. J. Ryan, J. M. Samson, S. A. Seligman, N. G. Steere, Doreen P. G. Stewart, R. H. Syred, J. H. Taylor, Gytha Wade, Pearl A. Aalker, Jayaweera Bandara Wedande, C. R. Whitfield, A. C. Wilson.

Research Defence Society

On Tuesday, Nov. 17, at 5.30 P.M., at University College, London, Gower Street, W.C.1, Sir Solly Zuckerman will give the Stephen Paget lecture. He will speak on the inevitability of science.

Royal College of Physicians of London

On Oct. 19 the Bisset Hawkins medal was presented to Dr. Percy Stocks for his contributions to the " epidemiological study of disease in this country, and to the improvements he has effected in statistical recording in the international field." The citation continued:

" After a distinguished career at Cambridge and Manchester, and experience of school health work at Bristol, Percy Stocks was appointed reader in medical statistics in the University of London. Later he was selected for the post of chief medical statistician to the General Register Office. Here, he introduced methods of measuring morbidity in order to supplement the decreasing information obtained from the falling mortality rates. Since his retirement he has continued his work, as senior research fellow for the British Empire Cancer Campaign. His analyses of the regional and local distribution of cancer mortality in this country have been very illuminating, and have revealed some curious anomalies such as the great excess of carcinoma of the stomach in North Wales. His development of a cancer registration system to display the epidemiological features of the disease is proving a most useful tool, not only in England and Wales but in other countries. Percy Stocks' latest studies on the population of Lancashire and the West Riding of Yorkshire have provided evidence to show that, in addition to cigarette smoke, some part in the genesis of bronchitis and of cancer of the lung is played by atmospheric pollution."

The Baly medal was presented to Dr. Ivan de Burgh Daly. The citation was as follows:

" Ivan de Burgh Daly's research career began immediately after the first world war at University College London where, in Professor Starling's laboratory, he learnt the disciplines on which his subsequent work on the cardiovascular system was founded. Later, Daly began an intensive attack on the problem of the factors governing the flow of blood through the lungs. Having established the importance of the bronchial circulation for the study of pulmonary vasomotor nerve function in isolated lungs and the criteria which must be satisfied before an active vasomotor control of the lesser circulation can be substantiated, Daly proceeded to an investigation of pulmonary vasomotor nerve function and the pathway and nature of the fibres subserving it in the whole animal. For this purpose he devised the 'perfused living animal' preparation in which the greater and lesser circulations were separately maintained and controlled by two blood pumps which were substituted for the heart. Daly's success with this preparation undoubtedly stimulated and influenced the later development of open-heart surgery. Thereafter he collaborated with his son Michael de Burgh Daly, in modifications of his 'perfused living animal' preparation. Daly's researches over the past 40 years in Birmingham, Edinburgh and Cambridge form a fascinating sequence of logically planned and rigidly controlled investigations which have not only made outstanding contributions to physiological knowledge but also exposed the criteria that must be satisfied in order to ensure the sound interpretation of present and future data on the dynamics of the pulmonary circulation."

The Order of St. John of Jerusalem

On Oct. 22 the following investments were made to this order:

As Commanders.—J. C. N. Wakeley, F.R.C.S., W. H. Shilvock, M.B., E. H. Eastcott, L.R.C.P.E., T. E. Wood, M.R.C.S., J. M. Russell, M.B., Surgeon Rear-Admiral W. R. S. Panckridge, M.R.C.S., Q.H.P., W. K. Hay, M.B.

As Officers.—G. M. Lloyd, M.R.C.S., N. V. M. Dodds, M.B., Surgeon Captain B. S. Lewis, D.S.C., M.R.C.S.

Commission of Neurochemistry

This commission of the World Federation of Neurology met for the first time in Antwerp on Sept. 29 and 30. The commission plans to establish a registry of neurological material available for neurochemical investigation. Further particulars may be had from the secretary of the commission, Dr. A. Lowenthal, Institut Bunge, 59, Rue Philippe Williot, Berchem-Anvers, Belgium.

A symposium on neurochemistry is to be held in Rome during the Congress of Neurology in 1961. The two main topics of discussion will be lipids and lipoproteins and their metabolism, and disorders of myelin (excluding disseminated sclerosis).

Medical Director-General of the Navy

On April 30 Surgeon Rear-Admiral W. R. S. Panckridge will succeed Surgeon Vice-Admiral Sir Robert May as medical director-general of the Navy.

Mental Health Services

The Minister of Health has directed local authorities to submit their proposals for extending these services, under the new Mental Health Act, not later than April 1, 1960. He has also asked them to describe the services which they already provide, so that he may satisfy himself that a reasonable standard of care will be offered.

National Fund for Poliomyelitis Research

Grants made by this Fund during the third quarter of this year include: an additional £16,715 to the Oxford Regional Hospital Board for the establishment of a disabled-living research unit at the Nuffield Orthopædic Centre, Oxford, and £15,000 to the department of orthopædic surgery of Edinburgh University for the proposed new clinical unit at the Princess Margaret Rose Hospital.

British Institute of Radiology

The annual congress and exhibition will be held in Church House, Westminster, S.W.1, on Dec. 10 and 11. Sir Robert Platt will give the opening address, on the physician's outlook on genetics; and Dr. E. E. Pochin will give the Mackenzie Davidson lecture, on the examination of thyroid activity with radioiodine. The meeting will include symposia on small-bowel malabsorption states; therapy with beams of high-energy particles; large-volume irradiation, immunity response, and bone-marrow replacement; and radiology in stereotaxic cerebral surgery. Further particulars may be had from the general secretary of the institute, 32, Welbeck Street, W.1.

This year more space is available for the exhibition held in connection with the congress, and it will be possible to include instruments, apparatus, and models, as well as diagrams, charts, and films. Details of exhibits in radiodiagnosis should be sent to Dr. R. G. S. Ollerenshaw, Department of Medical Illustration, Royal Infirmary, Manchester, 13, and details of exhibits in radiotherapy, radiology, and physics should be sent to Dr. R. D. Hoare, Maudsley Hospital, Denmark Hill, S.E.5, by Oct. 30.

Medical Defence Union

Speaking at the annual general meeting in Dublin on Sept. 15, Dr. P. T. O'FARRELL, P.R.C.P.I., said that during 1958 the Union handled 2677 cases—183 more than in 1957. Though the Union protected the medical and dental professions from all kinds of hazards arising from practice, its chief financial commitments turned on the interpretation of the terms " reasonable skill and care "; which was often a matter of controversy, for it was not always recognised that the practice of medicine was not an exact science and that errors of judgment and faults in diagnosis and treatment must occasionally occur. The incidence of professional liability claims had increased considerably in the past twenty to thirty years, partly because of the complexities of modern medicine and partly because of the attitude of the public towards litigation. In 1958 the Union's solicitors dealt with 95 cases in which the primary issue was professional negligence. Of these, 12 were fought in Court (6 were won and 6 lost), 24 were settled by payment made fully or partly by the Union, and 59 were abandoned by the plaintiff or disposed of by some other party without any contribution from the Union.

The Union now has 46,656 members. At the end of 1958 the total funds available were £144,000. During the year expenditure exceeded income by £15,000. The full effects of the increase in subscriptions will be seen in the accounts for 1959, which are expected to show a surplus.

The president is Dr. S. Cochrane Shanks, and the hon. treasurer Dr. Henry Robinson. Dr. P. H. Addison has succeeded Dr. Robert Forbes as secretary. The address of the Union is Tavistock House South, London, W.C.1.

Extension to Dorset Mental Hospital

On Oct. 2 the Forston clinic was opened at Herrison Hospital, Dorchester, where it will be used as an admission unit. It has accommodation for 96 inpatients and also has treatment facilities for outpatients.

The degrees of M.B., CH.B. Glasg. which were received by R. L. C. Cumming (see *Lancet*, Aug. 15, p. 132) were awarded with commendation.

Dr. T. Hanley has been appointed medical adviser in the medical research department of the Wellcome Foundation Ltd.

The annual dinner of the Glasgow University Club, London, will be held at the Trocadero Restaurant, W.1, at 7.30 P.M. on Thursday, Nov. 26. The chairman will be Sir David Campbell, president of the General Medical Council. Graduates who are not members of the club should write to Dr. J. F. Heggie, Department of Pathology, North Middlesex Hospital, N.18.

The National Association for Mental Health last April held an inter-clinic conference on Truancy—or School Phobia? Copies of the proceedings (3*s.* 6*d.*) may now be had from the Association, 39, Queen Anne Street, London, W.1.

CORRIGENDA: *Prevention of Stillbirth in Rh Hæmolytic Disease.*—In this article by Dr. G. H. Tovey and Dr. Timos Valaes (Oct. 10, p. 521) in the section headed First-affected Babies a line was omitted in the first sentence of the third paragraph. It should have read: "Including the neonatal deaths, the pregnancy ended in a dead baby in approximately 1 in 3 cases when the antibody titre was at or above 1/40, compared with approximately 1 in 30 cases at a titre of 1/10 to 1/20".

A General Theory of National Expenditure on Medical Care.—In fig. 1 of this article by Dr. J. R. Seale (Oct. 10, p. 555) the numerals for medical-care expenditure shown on the ordinate should have read 0, 4, 8, 12 and 16.

Diary of the Week

OCT. 25 TO 31

Monday, 26th

UNIVERSITY OF LONDON
5.30 P.M. (University College, Gower Street, W.C.1.) Prof. A. Fleckenstein (Freiburg): Isotopic Studies of Phosphorus Metabolism in Skeletal and Heart Muscle. (First of two lectures.)
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. M. D. Milne: Disorders of Potassium Metabolism.
HUNTERIAN SOCIETY
8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Mr. A. W. Badenoch: Drops of Water—Grains of Sand. (Presidential address.)
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Prof. D. A. K. Black: Treatment of Renal Disease.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Prof. I. G. W. Hill: Some Problems in Hæmodynamics and Heart-failure.

Tuesday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. K. M. Backhouse: Gubernaculum Testis Hunteri, Testicular Descent and Maldescent. (Arris and Gale lecture.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Dr. E. R. Cullinan: Ulcerative Colitis—the Present Position. (Presidential address.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. W. Mayer-Gross: Psychological Action of Drugs and the Methods of its Investigation.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Detection and Measurement of Radiation and Radioisotopes. (First of two lectures.)
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. M. P. Embrey: Tocographic Study of Uterine Mobility.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. A. M. Cooke: Medical Writing.
ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine.) *Medical section.* Mr. W. Haenszel (Bethesda): Problems in the Estimation of Familial Aggregation of Disease.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Sir Geoffrey Jefferson: The Basis of Consciousness.

Wednesday, 28th

UNIVERSITY OF LONDON
5.30 P.M. (University College.) Professor Fleckenstein: Isotopic Studies of Phosphorus Metabolism in Skeletal and Heart Muscle. (Second of two lectures.)
ROYAL COLLEGE OF SURGEONS
5 P.M. Mr. D. Greer Walker: John Hunter—Order Out of Variety. (Arnott demonstration.)
ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Prof. T. Russell Fraser, Mr. A. P. M. Forrest, Dr. D. N. Baron: Assessment of Endocrine Function after Hypophysectomy or Pituitary Destruction.
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Prof. R. A. McCance: Chemical Stability in the Newborn Period.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.30 P.M. Dr. Klaus Schwarz (Bethesda): Experimental Necrotic Liver Injury.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Skin Cancer.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. F. H. Scadding: Intrathoracic Cysts.
MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine.* Prof. Stanley Alstead: Therapeutics, Medicine, and the Future.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. W. W. Park: Embolism Within the Pulmonary Circulation.

Thursday, 29th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. H. R. Thompson: Sergeant Surgeons to Their Majesties (Thomas Vicary lecture.)
ROYAL SOCIETY OF MEDICINE
10 A.M. All-day symposium on atherosclerosis.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. J. H. Wilkinson: Blood Enzymes in Diagnosis.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. H. R. Vickers: Dermatitis in Industry.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M. Dr. R. L. Vollum: Antibiotics in Current Practice.
UNIVERSITY OF LIVERPOOL
5.15 P.M. (With Liverpool Medical Institution.) Sir Ernest Finch: The Romance of Surgery.
HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh, 8.) Prof. J. I. P. James: Early Treatment of the Injured Hand.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. I. E. Bush: Use of Chromatography for Estimating and Identifying Substances of Biological Interest.

Friday, 30th

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. Alan Parks: Ætiology and Treatment of Fistula-in-ano.
4 P.M. Prof. J. R. Squire: Phenylketonuria.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
5.30 P.M. Dr. Paul C. Bucy (Chicago): Neural Mechanism Responsible for the Control of Motor Activity.
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Queen Charlotte's Hospital, Goldhawk Road, W.6.) Miss D. M. Shotton: An Emergency Maternity Service—the Place of the Flying Squad.
PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Mr. G. Lloyd-Roberts: Common Orthopædic Problems in the Young.

Appointments

BERNSTEIN, D. C., B.M. Oxon., D.M.R.D.: assist. radiologist, St. Thomas's Hospital, London.
DAVISON, WILLIAM, M.B. Edin., M.R.C.P.E.: part-time consultant geriatric physician, United Cambridge Hospitals and East Anglian Regional Hospital Board.
GLYNN, CHRISTINA C., M.B. N.U.I., D.C.H.: maternal and child welfare M.O., Derbyshire.
GRAHAM, J. L., M.B. St. And., D.OBST.: assistant M.O., student health service, University of Sheffield.
JENKINS, D. C. W., M.B. Lond., D.P.M.: assistant psychiatrist (S.H.M.O.), Ely Hospital, Cardiff.
MACDONALD, J. S., M.B. Edin., D.M.R.D.: assistant radiologist, St. Thomas's Hospital, London.
PARE, C. M. B., M.D. Cantab., M.R.C.P., D.P.M.: consultant physician, department of psychological medicine, St. Bartholomew's Hospital, London.
SCHOFIELD, C. B. S., M.D. Durh., M.R.C.P.: consultant venereologist, Tyneside area hospitals.
SUMERLING, M. D., M.B., B.SC. Leeds, M.R.C.P., D.M.R.D.: consultant radiologist, Royal Infirmary, Edinburgh.
WYBAR, K. C., M.D., CH.M., B.SC. Glasg., F.R.C.S., D.O.M.S.: consultant ophthalmic surgeon, Royal Marsden Hospital, London.

The Hospital for Sick Children, Great Ormond Street, Lond

DORMANDY, KATHERINE M., M.B. Lond., M.R.C.P.: senior registrar hæmatology and microbiology.
HARGROVE, R. L., M.B. Lond., F.F.A. R.C.S., D.A.: junior anæsthetic registrar.
JANSZ, A. W., M.B. Ceylon, F.R.C.S.: house-surgeon.
LOCK, S. P., M.B. Cantab.: registrar in clinical pathology.
MARSHALL, W. C., M.B. Sydney, D.C.H.: assistant medical registrar.
MOYNAHAN, E. J., F.R.C.P.: consultant in dermatology.
NORMAND, I. C. S., B.M. Oxon., M.R.C.P.: house-physician.
RYAN, ELIZABETH A., M.B. Lond., M.R.C.P.: part-time M.O. in dermatology.
WILSON, VICTOR, M.B. Lond.: part-time M.O. in dermatology.

Birmingham Public Health Department:

BUCKLEY, MARGARET E., M.B. N.U.I., D.P.H.: assistant M.O.
HOLLANDS, MARGARET, M.B. Birm., D.C.H.: assistant M.O.
ROGERSON, E. ELIZABETH, M.B. Birm.: assistant M.O.

Buckinghamshire County Council:

BURNE, B. H., M.R.C.S., D.P.H.: senior assistant M.O.
HERDMAN, PATRICIA, M.B. Lond., D.P.H.: senior M.O.
JENNINGS, ETHEL G., M.B. Dubl.: assistant M.O.
VENNING, MARY R., B.M. Oxon.: assistant M.O.

Colonial Appointments:

EZIKE, C. A., F.R.C.S.E.: specialist (surgeon), Federation of Nigeria.
MACKICHAN, I. W., M.B. Cantab., D.P.H., D.T.M. & H.: D.M.S., Zanzibar.
MARCHANT, D. E., M.B. Lucknow, D.I.H., D.P.H., D.T.M. & H.: assistant M.O.H., health department, Trinidad.
PEARCE, J. A., M.B. N.U.I., D.O.: senior M.O. (clinical), Federation of Nigeria.
RAMAN, A. C. D. A., M.R.C.S., D.P.M.: specialist (psychiatry), health department, Mauritius.
TWOMEY, JOHN, M.B. N.U.I., D.T.M. & H.: M.O., Uganda.